

Investigation of Patient-Controlled Analgesia for the Treatment of Postoperative Pain in Children.

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DECLARATION

This thesis has been written by me and the work incorporated in it is my own. I was the principal investigator in all of the studies included in the thesis. Chapter 1 is based on a survey of the relevant literature. I was helped with the recruitment of subjects by Drs David Robinson (Chapter 2), Ian Harper (Chapter 3), Karen Mottart and Charles Marshall (Chapters 4 and 5) and Gordon Byers (Chapter 8). Drs Neil Morton and Roddie McNicol gave considerable advice in the planning and writing up of the studies. The clinical research was performed while I was a Research Fellow in the Department of Anaesthesia at the Royal Hospital for Sick Children, Yorkhill, Glasgow. The thesis was written while I was a Lecturer in the University Department of Anaesthesia at the Royal Infirmary of Edinburgh. The thesis has not been submitted in candidature for any other degree, diploma or professional qualification.

Edward Doyle.

ABSTRACT

The work incorporated in this thesis was conceived and carried out with the aim of investigating the efficacy and the incidence of side effects when different regimens for patient-controlled analgesia with morphine sulphate are used in children. Features of interest were the size of the bolus dose, the place of a background infusion and its magnitude, an alternative to the intravenous route of administration and the prevention of postoperative nausea and vomiting.

In a comparison of patient-controlled analgesia with and without a background infusion of 20 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate there were no significant differences in the pain scores of the two groups although there were more side effects in the background group. There was also a better sleep pattern in this group.

In a comparison of different background infusions, the inclusion of a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate did not increase the incidence of side effects and was associated with less hypoxaemia and a better sleep pattern than no background infusion, although it did not improve the efficacy of the technique. When pain was assessed after movement, the inclusion of a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ improved analgesia and was associated with less hypoxaemia and a better sleep pattern than no background infusion.

When bolus doses of 10 micrograms kg^{-1} and 20 micrograms kg^{-1} of morphine sulphate were compared, 20 micrograms kg^{-1} produced lower pain

scores and fewer hypoxaemic episodes than 10 micrograms kg⁻¹. There were no differences between the groups in the incidence of side effects.

In a comparison of intravenous and subcutaneous infusions of morphine sulphate for the treatment of postoperative pain there were no differences between the groups in pain scores or the incidence of side effects. The subcutaneous route appears to be as effective and safe as the intravenous route for the administration of opioid infusions in children undergoing elective surgery. In a comparison of the intravenous and subcutaneous routes of administration for patient-controlled analgesia, the subcutaneous group had a significantly greater percentage of valid demands for analgesia than the intravenous group. There were no differences between the pain scores of the two groups. The intravenous group suffered significantly more hypoxic episodes than the subcutaneous group. There were no differences between the groups in the incidence of side effects. Subcutaneous patient-controlled analgesia appears to be as effective and safe as intravenous patient-controlled analgesia.

When transdermal hyoscine was compared with placebo for the prevention of postoperative nausea and vomiting associated with patient-controlled analgesia, there was a significant reduction in the incidence of postoperative nausea and vomiting in the treated group compared with the placebo group. The treated group had a significantly increased incidence of sedation and dry mouth.

CHAPTER ONE

Background to the Use of Patient- Controlled Analgesia in Children.

Postoperative Analgesia in Children

There is convincing evidence that until the mid to late 1980s postoperative pain in children was substantially under treated compared with the practice in adults and that most children undergoing surgery suffered considerable and unnecessary pain while in hospital [Eland and Andersen, 1977; Beyer et al, 1983; Mather and Mackie, 1983; Schechter, 1989]. This situation occurred during a period when the treatment of postoperative pain in adults is widely acknowledged to have been grossly inadequate. The reasons for this state of affairs included a persistent and now discredited belief that neonates and infants do not feel pain, a general lack of interest in the subject apart from the efforts of a small number of interested anaesthetists, fear of the side effects of analgesic drugs and difficulties in the assessment of pain in children. The situation was compounded by frequent poor prescribing in terms of dosages and their frequency of administration. Children often received smaller doses of analgesics than adults on a dose to weight basis which were administered at longer intervals. When doses were prescribed on a *pro re nata* or *as required* basis they were often administered in the smallest dose prescribed [Marks and Sacher, 1973]. After equivalent surgical procedures, children were usually given weak analgesic at an earlier stage in the postoperative course than adults [Beyer et al, 1983; Mather and Mackie, 1983; Schechter et al, 1986].

Few people now believe that neonates and small infants do not feel pain. Apart from common sense there is a wealth of scientific evidence to support the suggestion that neonates and infants can and do experience pain. There is evidence to suggest that the complete nervous system is active during foetal life [Valman and Pearson, 1980; Flower, 1985] and the relevant neuroanatomical, neurophysiological and neurochemical mechanisms are mature enough in term and premature neonates for them to experience pain. The density of cutaneous pain receptors is at least the same in neonates as

in adults [Anand and Hickey, 1987]. Neurological tracts in the spinal cord and brain involved in the central transmission of pain are completely myelinated from the end of the third trimester [Pounder and Steward, 1992]. Substance P and its receptors are detectable in the foetal dorsal horn from 12-16 weeks of gestation [Charnay et al, 1987; Marti et al, 1987]. Endogenous opioids are present in the plasma [Shaaban et al, 1982] and cerebrospinal fluid [Orlowski, 1986] of term infants and their concentrations increase in response to stress. Increases in heart rate, blood pressure and palmar sweating together with decreases in arterial oxygen saturation are observed in neonates undergoing painful procedures such as circumcision [Holve et al, 1983; Williamson and Williamson, 1983] or heel lancing [Owens and Todt, 1984; Johnson and Strada, 1986] without anaesthesia and these changes can be prevented by providing analgesia with a local anaesthetic technique [Holve et al, 1983; Williamson and Williamson, 1983; Maxwell et al, 1986]. The altered behavioural patterns seen after these procedures [Emde et al, 1971; Anders and Chalemian, 1974; Marskall et al, 1980] are not seen if local anaesthesia is used to provide analgesia during the procedure [Dixon et al, 1984]. In neonates and infants undergoing surgical procedures with minimal anaesthesia there is an increased release of catecholamines, glucagon, cortisol and growth hormone [Obara et al, 1984; Anand et al, 1985; Milne et al, 1986; Srinivasan et al, 1986] in response to these procedures and this is attenuated when potent analgesia is provided [Anand et al, 1987]. Repetitive noxious stimulation in neonates is able to generate hyperalgesia and persistent increases in the excitability of the spinal cord and analgesia can prevent this process [Fitzgerald, 1984; Andrews and Fitzgerald, 1994]. There is also evidence to suggest that untreated pain during the neonatal period may increase the degree of pain experienced during subsequent invasive medical procedures [Taddio et al, 1995]. In summary, the neural pathways and neurotransmitters responsible for the perception of pain and its modulation are present in the neonate and the evoked hormonal, metabolic and behavioural responses are similar to

those seen in older children and adults. It is essential, therefore, to provide adequate analgesia in all children undergoing surgery.

The Joint Colleges Report on Pain after Surgery from the College of Anaesthetists and the Royal College of Surgeons in 1990 drew particular attention to the inadequacy of pain relief in children where the traditional beliefs and practices which limit the provision of adequate analgesia were particularly marked. The report made several recommendations aimed at improving the treatment of postoperative pain. These included improving the education of medical and nursing staff in pain management, the establishment of an acute pain service in all major hospitals and the systematic assessment and recording of pain after surgery.

The Assessment of Pain

The treatment of pain should be directed by valid assessments of pain to ensure, as far as possible, efficacy without the occurrence of unnecessary side effects. A pain assessment tool should be able to detect the presence of pain, to estimate its severity and to determine the effectiveness of analgesic interventions. In children who old enough to communicate self-report numerical [Maunuksela et al, 1987] or visual analogue [Berde et al, 1991] scales as used in adults have been shown to fulfill these requirements and as subjective reports of pain by the patient are preferable to assessments made by medical or nursing staff. Graded scales using drawings or photographs of facial expressions as well as colour scales and body charts have been described for use in children aged three to six years but are not widely used. In babies, infants and handicapped children subjective assessments are not possible and pain assessment is based upon indirect indicators. Pain assessment tools used in these groups are based on behavioural, physiological or biochemical indicators. Of the behavioural

assessments facial expression has been systematically coded for neonates [Grunau and Craig, 1987] and an objective pain score has been validated in toddlers undergoing groin surgery [Hanallah et al, 1987]. Of the physiological parameters, changes in heart rate and blood pressure and a reduction in respiratory sinus arrhythmia have been shown to be useful in term neonates and infants but not in the premature infant [Porter et al, 1988]; a reduction in transcutaneous pO₂ and an increase in palmar sweating have also been shown to occur when invasive procedures are performed in neonates without anaesthesia. Measurements of hormones such as cortisol, adrenaline, growth hormone and renin known to increase during stress have been investigated but are not useful in routine clinical work because of the practical difficulties of sampling, delay and their limited relevance to pain as opposed to stress. On a practical day to day level children who are able to communicate should be asked to score pain using a simple four point self report scale during a movement such as a deep breath or cough (which is a more sensitive discriminator than assessments performed at rest) - 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain. Younger children should be observed by experienced paediatric nurses and scored using a similar scale - 0 = pain free; 1 = comfortable except on moving; 2 = uncomfortable at rest; 3 = distressed but can be comforted; 4 = distressed and inconsolable [Lloyd-Thomas and Howard, 1994]. In most cases patients should be pain free at rest and have minimal discomfort during movement. During treatment for acute pain assessments should be performed hourly to ensure efficacy.

Opioids for Postoperative Pain in Children

Options for the treatment of pain in children include physical, psychological and pharmacological methods. Simple measures such as ensuring warmth,

swaddling and feeding if appropriate may all be useful. The presence of parents, reassurance and distraction are also important. Older children should be given a simple preoperative explanation of what is to happen and an assurance that any pain experienced will be treated as well as possible. The main groups of drugs used for analgesia after surgery or trauma are the same as in adults - opioids, local anaesthetics and non-steroidal anti-inflammatory drugs including paracetamol.

Opioids are a versatile and widely used group of analgesic drugs and are the mainstay of analgesia for most children undergoing intermediate and major surgery. These drugs interact with three classes of membrane receptors first described in 1973 [Pert and Snyder, 1973] which are widespread throughout the central nervous system. Structurally, these receptors are proteins known as G protein-coupled receptors which constitute 80% of known membrane receptors. These receptors consist of seven peptide subunits and span cell membranes. The primary effect of opioid receptor activation is a reduction in neurotransmission. This is produced by presynaptic inhibition of neurotransmitter release, although there may also be postsynaptic inhibition of evoked activity. Receptor activation causes increased potassium conductance across the nerve cell membrane (and hence hyperpolarisation), calcium channel inactivation or both with a reduction in neurotransmitter release [Atcheson and Lambert, 1994]. There are also peripheral actions of opioids. Opioid receptors exist on the peripheral ends of primary afferent neurones and their activation may directly decrease neurotransmission or inhibit the release of excitatory neurotransmitters such as substance P. There is clinical evidence in support of a clinical role for opioids as peripheral analgesics [Stein et al, 1993].

There are three subtypes of opioid receptor known as mu, kappa and delta receptors. Mu receptors are associated with analgesia, respiratory depression, euphoria, sedation and physical dependence [Vaught et

al, 1982]. Kappa receptors are located mainly in the spinal cord and are responsible for analgesia produced at cord level and dysphoria [Wood, 1982; Snyder, 1984]. Delta receptors mediate respiratory depression caused by exogenous opioids although their physiological role is unclear [Pleuvry, 1991]. The endogenous ligands for these receptors are three groups of structurally related opioid peptides which bind to the receptors. These are beta-endorphin, dynorphin related peptides and the enkephalins.

The most commonly used opioid is morphine sulphate and there is more clinical experience with this in children than with any of the other opioids. As well as producing analgesia the various opioids produce a similar spectrum of side effects. At equipotent analgesic doses all the pure agonist opioids produce similar degrees of respiratory depression, sedation, euphoria, nausea, and constipation [Jaffe and Martin, 1985]. They have the disadvantage of a relatively narrow therapeutic range and marked variability in response between patients because of pharmacokinetic and pharmacodynamic variability. This is particularly marked in children aged less than three months where drug elimination is very variable with diminished clearances and prolonged half-lives [Koren et al, 1985; Koehntop et al, 1986; Greeley et al, 1987; Lynn and Slattery, 1987; Singleton et al 1987]. In neonates and young infants the volume of distribution of opioids is greater than in older children [Greeley et al, 1987], the blood-brain barrier is more permeable [Kupferberg and Way, 1963; Sanner and Woods, 1965], there are reduced plasma protein concentrations (especially alpha-1-acid glycoprotein) with consequent high levels of free drug [Morselli et al, 1980] and there may be a preponderance of Mu 2 receptors which mediate respiratory depression caused by opioids [Pasternak et al, 1980; Leslie et al, 1982]. Clinically, there is undoubtedly an increased sensitivity to the depressant effects of opioids in the first three months of life [Way et al, 1965; Koren et al, 1985; McNicol, 1994]. After this the enzymatic pathways responsible for opioid metabolism mature [Koren et al 1985; Olkkola et

al, 1988] and the pharmacokinetics of opioids become more like those of adults [Dahlstrom, 1979; Hertzka, 1987]. They may be administered more liberally with safety in these older infants. With sensible dosage regimens and appropriate monitoring, the use of opioids in healthy children older than three months provides excellent analgesia with a wide margin of safety although problems may still occur if they are used in an inappropriate manner [Gourlay and Boas, 1992; Wolf, Lawson and Fisher, 1995].

There are, of course, older children who can be expected to be particularly susceptible to the depressant effects of opioids because of specific diseases or sensitivities e.g. those with severe respiratory disease, upper airway obstruction and renal or hepatic impairment. The concurrent administration of other centrally acting sedative drugs with opioids puts the patient at considerable risk of over sedation and respiratory depression.

The analgesic effect of opioids depends on the brain concentration of active compounds which is related to plasma levels. Intermittent intramuscular administration is unlikely to produce steady plasma levels [Austen et al, 1980; Grabinski et al, 1983] and may result in widely fluctuating plasma levels of opioids. This tends to produce periods of analgesia and excessive sedation alternating with periods of inadequate pain relief [Angell, 1982; Berde, 1989]. Intermittent intramuscular injections may cause such distress to children that they are not requested [Eland and Andersen, 1977]. These factors, combined with the need for two qualified nurses to administer a dose of analgesic, may lead to long periods of inadequate pain relief when intermittent intramuscular injections are used to provide analgesia in children.

The intermittent administration of intravenous bolus doses of an opioid on an as required basis has the potential to provide extremely good analgesia with a high degree of safety. If pain is assessed conscientiously and analgesia

given when required then excellent analgesia can be achieved which takes account of the great variability in patient requirements which arises because of pharmacokinetic and pharmacodynamic factors. This method of administration has the further advantage of requiring assessment of the patient before a dose of opioid is given and avoiding obligatory opioid administration irrespective of the condition of the patient. Because it is a relatively labour intensive method of administering opioids, intermittent bolus dose administration is rarely used. Despite this it is a very useful and safe method of giving analgesia to children especially neonates and premature babies, for the early treatment of pain following trauma in Accident and Emergency Departments and in the immediate postoperative period in the recovery area.

Opioids by Infusion in Children

The technique of continuous intravenous infusion of an opioid solution has become popular because of its efficacy, simplicity and wide range of indications. Continuous infusion will maintain a steady blood concentration of opioids once equilibration is reached and avoids the need for repeated injections. A loading dose is required to avoid the prolonged period of four to five half lives required to reach a steady state. The efficacy of this technique in children has been shown in several series. Beasley and Tibbals used infusions of 10-40 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ in 121 children undergoing major surgery with no significant respiratory depression (although this was assessed by four hourly respiratory rates). In 44 children from 14 months to seventeen years infusions from 10-50 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ were effective with mild hypercarbia seen in three children receiving 40-50 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ [Lynn et al, 1984]. Dilworth and McKellar reported a series of 144 patients from 6 months to 15 years receiving papaveretum 50-70 micrograms

$\text{kg}^{-1} \text{ hour}^{-1}$ and noted bradypnoea in 5% of subjects. The technique of an infusion following a bolus dose has been demonstrated to provide better analgesia than intramuscular injections [Bray, 1983; Hendrickson et al, 1990]. An intravenous infusion of 10-40 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate following a bolus of 150 micrograms kg^{-1} provided equivalent analgesia to an epidural infusion of 0.1-0.4 ml hour^{-1} of 0.25% bupivacaine in infants undergoing abdominal surgery [Wolf and Hughes, 1992]. In this study patients receiving a morphine infusion had a lower respiratory rate than those receiving an epidural infusion but this was not clinically significant and was not associated with hypoxia while breathing air. Continuous intravenous infusion of papaveretum up to 37.5 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ in infants between four weeks and six months of age provided very good analgesia with only one incident of clinically significant hypoventilation detected by continuous pulse oximetry while breathing air [Jones and Stokes, 1991].

The technique of a continuous intravenous opioid infusion is suitable for children younger than 7-8 years and older children who are unable to use patient-controlled analgesia. Dosages in the range 10-40 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine are adequate in most patients and infusions are usually started in the middle of this range for children over six months and at 5-10 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ for those younger.

The effective use of intravenous infusions requires close nursing supervision to ensure that the infusion rate is adequate and titrated against needs which will change with time and activity such as mobilisation and physiotherapy. Because of the obligatory opioid administration without patient assessment and feedback which is inherent in an infusion technique there is a necessity to monitor patients closely to assess efficacy and prevent the occurrence of side effects particularly respiratory depression and over sedation. There is also a danger of excessive drug administration because of incorrect drug dilutions, machine malfunction or incorrect programming of the pump. If

infusions are administered through the same intravenous cannula as intravenous fluids there is a danger that opioid will reflux into the intravenous fluids and a subsequent uncontrolled bolus may be delivered. To prevent this infusions should be administered via a dedicated cannula or an anti-reflux valve.

An alternative method of delivering a continuous infusion of an opioid is to use the subcutaneous route of administration. This technique has been shown to be effective in adults [Hindsholm et al, 1993] and children [McNicol, 1993]. It is subject to the same potential dangers as the intravenous route.

Patient-Controlled Analgesia

Patient-controlled analgesia is an analgesic technique whereby the patient is able to self-administer bolus doses of opioid with a degree of flexibility within a prescription which sets the bolus dose administered, the obligatory delay between boluses (lockout interval), the presence or absence of a background infusion and, usually, a maximum dosage over a period of four hours. Most machines comprise an infusion pump with software allowing the use of a trigger device to deliver bolus doses with or without a variable background infusion [Abbott Laboratories Ltd; Graseby Medical Ltd; Bard International Ltd; IVAC; Kabi Pharmacia]. Mechanical patient-controlled analgesia machines such as the Baxter infusor [Baxter Healthcare Ltd] and the Vygon Freedom PCI Set [Vygon (U.K.) Ltd] make use of a depot chamber which is filled by a pressurised infusor or a vacuum and controlled by a spring loaded clamp. The time taken for the depot chamber to fill comprises the lockout interval [Mackey et al, 1993]. These devices have been used successfully in children [Irwin, Gillespie and Morton, 1992]. There

are also compact battery powered units available for mobile patients which have a role in terminal care and chronic pain [Chrubasik, 1984; Wermeling et al, 1987].

The Development of Patient-Controlled Analgesia

The principle of patient-controlled analgesia developed in the 1960s as a result of attempts to measure or quantify postoperative pain in psychological studies [Sechzer, 1968]. Patients were instructed to press a button and inform a nurse when they felt pain and required analgesia. This was delivered by the nurse using a spring loaded clamp on an infusion line and the opioid consumption was noted. A benefit of this method of assessing pain was noted to be excellent analgesia. Apart from the efforts of a few enthusiasts, there was little subsequent interest in this technique for nearly twenty years because of a lack of interest in the treatment of postoperative pain, the introduction of epidural infusions for much major surgery and the lack of suitable reliable equipment. A hand held spring loaded clamp controlling a pethidine infusion was used for obstetric analgesia [Scott, 1970]. Sechzer went on to employ a fixed rate roller pump with two electro-mechanical timers [Sechzer, 1971]. This device demonstrated the important features of modern patient-controlled analgesia machines - the patient made a demand for analgesia by pressing a button, there was a fixed bolus dose given in response to this demand (controlled by the first timer) and there was a refractory period during which no further doses would be administered (controlled by the second timer). Devices based on a syringe driver appeared [Keeri-Szanto, 1971; Evans et al, 1976]. A device controlled by a microprocessor was developed and was commercially available for a period as the On-demand Analgesic Computer (ODAC) [Hull and Sibbald, 1981; Hull, 1985]. With the development of commercially available pumps capable

of delivering accurately the small boluses required with lockout intervals and simultaneous interest in improving the standard of postoperative analgesia, patient-controlled analgesia rapidly became a common analgesic technique.

When used appropriately patient-controlled analgesia has the potential to provide good analgesia which is flexible enough to respond to the changing needs of patients with time and to take account of events such as physiotherapy and mobilisation with the prophylactic administration of a bolus. The technique should also take account of the great variability between patients in terms of the perception of pain and their pharmacokinetic and pharmacodynamic variability. Patients who perceive pain requiring treatment are able to self-administer within the limits of the prescription without reference to medical or nursing staff and their perception of the patient's distress. Doctors and nurses have been found to consistently underestimate the degree of pain compared with simultaneous patient assessments in adults [Klopfenstein et al, 1995] and children [Weldon, 1991]. Patients who metabolise opioids rapidly or who have a degree of pharmacodynamic resistance will be able to self administer more frequently than others who require less opioid while both groups receive adequate analgesia and remain satisfied.

The efficacy of patient-controlled analgesia has been well documented in adult practice and it has been shown to be superior to intermittent intramuscular injections [Keeri-Szanto, 1972; White et al, 1979; Slattery et al, 1983; Atwell et al, 1984; Wasylak et al, 1990; Boulanger et al, 1993] and to provide comparable analgesia to an epidural infusion of local anaesthetic [White et al, 1979] or to epidural opioids [Rosenberg, Heino and Scheinin 1984; Stoddart et al, 1993]. There is evidence that the optimal use of patient-controlled analgesia after major surgery is associated with less postoperative morbidity and earlier discharge than the use of intermittent intramuscular analgesia [Wasylak et al, 1990] although this may also be the

case with other techniques which optimise postoperative analgesia after major surgery.

Since patient-controlled analgesia requires not only patient cooperation but active participation and a willingness to take responsibility for an aspect of hospital care, it may be expected that the influence of psychological factors on this method of analgesia will be profound. In patients undergoing the same operative procedure there is great variability in the definition, perception and tolerance of pain after the procedure. There is also great variability in the distress caused to individual patients by pain and in their willingness to communicate this to medical and nursing staff. It is known that the analgesic effects of a given dose of analgesic can be greater when self-administered as opposed to nurse-administered [Keeri-Szanto, 1979] and that non-pharmacological factors have a profound influence on the effectiveness of a given analgesic intervention [Keeri-Szanto, 1979]. The effect of anxiety on pain and its perception is profound and in many patients the ability to control their analgesia reduces anxiety and may be expected to decrease the intensity of the perceived pain [Bowers, 1968; Wilson and Bennet, 1984]. Other personality traits which are relevant include the degree of introversion or extroversion and neuroticism. Ethnic background, previous experience and beliefs about pain and surgery may all affect the perception of pain. It has been suggested that patients who attempt to deal with situations and threats by seeking information and mastery of situations (a vigilant coping strategy) will benefit from patient-controlled analgesia by gaining a measure of self-control over analgesic administration and the degree of discomfort suffered. It allows patients to titrate themselves to a situation where there is an acceptable balance between the degree of discomfort or pain experienced and opioid induced side effects particularly nausea and vomiting. Conversely, some patients are unwilling to use patient-controlled analgesia appropriately and perceive this method of analgesia as threatening and prefer infusion or nurse-administered

analgesia. Those who adopt avoidance type coping strategies may well feel threatened by patient-controlled analgesia [Wilson and Bennet, 1984]. It has been demonstrated that patients' coping styles for stress correlate well with the effectiveness of patient-controlled analgesia [Wilson and Bennet, 1984]. There is nothing published on the psychological aspects of patient-controlled analgesia in children.

Patient-Controlled Analgesia in Children

In paediatric practice, patient-controlled analgesia was first described in 1987 [Brown and Broadman, 1987] in a series of adolescents aged 11-19 years undergoing orthopaedic, abdominal and thoracic surgery. This and several other descriptive series of patients [Dodd et al, 1988; Means et al, 1988; Rogers et al, 1988; Broadman et al, 1989, Gaukroger et al, 1989; Broadman et al, 1990; Lawrie et al, 1990; Mowbray and Gaukroger, 1990] demonstrated the efficacy of patient-controlled analgesia in suitable children and led to its wider use. Demonstration of the superiority of patient-controlled analgesia to intermittent intramuscular injections soon followed. Berde et al randomised children aged 7-19 years undergoing orthopaedic surgery to receive intermittent intramuscular injections of morphine 100-180 micrograms kg^{-1} three hourly as required for pain or patient-controlled analgesia with a bolus dose of 25 micrograms kg^{-1} and a lockout interval of 10 minutes with a four hourly maximum of 240 micrograms kg^{-1} . Pain was assessed by patient and nurse visual analogue scales and was significantly less in the group receiving patient-controlled analgesia than in the group with intramuscular injections [Berde et al, 1991]. A paediatric study comparing patient-controlled analgesia using morphine with a continuous infusion of morphine has demonstrated better pain relief with patient-controlled analgesia in appropriate patients [Bray et al, 1995].

Patient selection for patient-controlled analgesia depends on a number of features including the age of the child, their developmental stage and intelligence. The only absolute requirements are the ability to understand the concepts of demand analgesia and a lockout interval and to be physically able to operate the trigger of the patient-controlled analgesia machine. Features which may affect the suitability of the child for patient-controlled analgesia include the attitude of the parents, previous experience, unwillingness to be involved in their own care and the severity of illness. With adequate explanation and postoperative supervision many children aged 8 years and over can use patient-controlled analgesia appropriately as can some younger children down to five years of age although problems are more common in younger children. Appropriate and sensible use of a patient-controlled analgesia machine requires preoperative tuition of the child and parent(s) and postoperative reinforcement of this tuition particularly the concept of a lockout interval. Children should never be guaranteed complete analgesia from patient-controlled analgesia after surgery.

Most patient-controlled analgesia pumps designed for adult use are suitable for paediatric use. There does not seem to be a need for dedicated paediatric models. Most units prefer to vary the dilution of the opioid solution and maintain a constant volume in the syringe to permit dose administration on a mg kg^{-1} basis in a constant volume. Children old enough to use patient-controlled analgesia are usually able to press the trigger of most patient-controlled analgesia machines and modified triggers are available if necessary. Single use patient-controlled analgesia devices are available but they are relatively inflexible and expensive. Most units prefer to use electronic machines where the cost per patient is less and there is the facility to vary the settings from a standard recipe if required. Models should be lockable to prevent misappropriation of the syringe and prevent unauthorised changes in the settings. The facility to store data on usage of

the machine, opioid consumption and the numbers of valid demands which can be retrieved or down loaded is useful for research and audit purposes.

Safety Aspects of Patient-Controlled Analgesia

There are a number of potential problems associated with the use of patient-controlled analgesia in children. Inappropriate patient selection is likely to result in failure of the technique to provide analgesia and may lead to inappropriate use and excessive opioid consumption with sedation and respiratory depression. Even with careful patient selection and conscientious preoperative tuition which is reinforced after surgery, there will be a number of children who do not use the pump appropriately and refuse to press the trigger, resulting in unrelieved pain, or who administer excessive and unnecessary opioid. If the situation does not improve after an explanation of more appropriate use, it is usually appropriate to change to a straightforward infusion technique. There is a perception that patient-controlled analgesia is safer than infusions of opioids because excess administration will produce somnolence which prevents subsequent self administration of opioid. This is true to a degree but the safety is relative and not absolute since various factors may bypass this inherent safety of the technique.

The potential problems which may occur can be divided into those due to errors by medical and nursing staff, misuse by the patient or others and faults in the equipment.

Errors may be made in the dilution of opioid used for the pump (this should always be checked by a second person), in programming the device [White, 1987], in priming the pump and in the omission or misplacement of an anti-reflux valve. When changing syringes or cartridges there is the potential for

inadvertent bolus dose administration if the tubing to the patient is not clamped or closed during the change [White, 1987].

If people other than the patient press the trigger then the technique loses its inherent safety [Lam, 1993]. There may be intentional meddling with the pump by the patient or others [Stevens et al, 1991; Youngs, 1993]. Because of inadequate preoperative education or forgetfulness, patients may self-administer excessive doses of opioid [Johnson and Daugherty, 1992]. The mistaken use of a patient-controlled analgesia trigger as a nurse call device has been described resulting in excessive opioid administration [Farmer and Harper, 1992; Morton, 1993].

Patient-controlled analgesia pumps may malfunction and deliver more or less opioid than intended because of a software malfunction or external electrical power surges despite 'self-checking' facilities built into the software [Nottcutt et al, 1992]. There is a risk of reflux if a dedicated cannula is not used. A combination of a break in the continuity of the opioid delivery system and positioning of the opioid containing syringe above the patient may cause a gravity-fed syphon effect where all the available opioid is delivered to the patient as a bolus [Thomas and Owen, 1988]. Disengagement of the syringe from the driving mechanism may have the same result [Grover and Heath, 1992]. Manufacturing faults in single use disposable devices have been reported which would produce a rapid large delivery of opioid to the patient [Costigan, 1994]. Failure to remove the priming plate supplied with the Baxter single use device or the exertion of continual pressure on the patient control button converts the device to a constant infusion pump [Arnstein, 1994]. The Vygon single use device may deliver as much as 50% more opioid than intended if demands for analgesia are made frequently during the lockout interval. This occurs because filling of the reservoir chamber is non-linear and is 90% complete within three minutes while complete filling takes five minutes which is the nominal lockout time of the device. Frequent

demands for analgesia during the lockout interval will lead to the delivery of more opioid than prescribed [Smith, 1995]. In the presence of hypovolaemia, normal bolus doses of opioid may be excessive and may cause significant respiratory depression [Owen et al, 1988].

As with all opioid based techniques, the side effects of opioids are a potential problem. The most dangerous of these is respiratory depression but over-sedation, nausea and vomiting, urinary retention and pruritis are all possible. In the absence of a dedicated Acute Pain Service, the burden of preoperative preparation and postoperative supervision may be considerable. Despite these theoretical and actual problems with the use of patient-controlled analgesia in children, the technique is very safe in clinical practice when used and monitored appropriately. In the largest reported series of over 1500 children receiving patient-controlled analgesia two children were given naloxone for somnolence and a low respiratory rate of 6-8 breaths minute⁻¹. Both of these children had received concurrent sedative medications during the use of patient-controlled analgesia [Wilder et al, 1992].

A Monitoring Protocol for the Use of Opioids in Children

The potential problems which can occur with opioid administration by any route necessitate the implementation of some form of monitoring protocol which will detect potential problems at an early stage and provide warnings which can be acted upon to prevent the situation deteriorating. A simple and effective protocol has been described for this purpose [Morton, 1993]. In the context of opioid administration by infusion or patient-controlled analgesia,

the features of interest are a measure of respiratory depression or hypoventilation, an assessment of the level of sedation or consciousness, opioid consumption and machine performance. The intermittent recording of respiratory rate has been shown to be a late and insensitive monitor of hypoventilation [Catley et al, 1985; Wheatley et al, 1990; Kluger et al, 1992] and this cannot be relied upon to give an early warning of this problem. The use of pulse oximetry while breathing air is a more sensitive monitor of hypoventilation [Hutton and Clutton-Brock, 1993] and in the absence of other causes of hypoxia such as impaired gas exchange, mild hypoxia (arterial oxygen saturation $\{S_pO_2\} < 94\%$) indicates mild hypoventilation. This may be a consequence of excess opioid administration or of pain limiting respiratory movements and discrimination between the two requires assessment of opioid consumption, pain scores and level of sedation. A subject in pain will be alert and unwilling to take a deep breath or cough while a subject who has received excess opioid will be sedated.

Somnolence caused by opioids tends to occur at an early stage and is a valuable early warning of excessive opioid administration. When used in conjunction with pulse oximetry this helps to discriminate between the possible causes of hypoxia. In patients breathing supplementary oxygen arterial oxygen saturation (S_pO_2) is not a useful monitor of hypoventilation and the level of sedation becomes the most important method of detecting excessive opioid administration at an early stage. To be used properly the measure of sedation should be as objective as possible to avoid bias between observers and with time. This should ensure that different observers looking at the same patient will give the same sedation score and that important changes in the status of the patient are reflected by changes in the score. The components of the Glasgow Coma Scale which relate to eye opening fulfil these requirements. There is a potential problem with discrimination between sleep and over sedation with concern being expressed that unless patients are woken regularly it is impossible to be

sure that they are not over sedated. With practice and experience paediatric nurses can usually discriminate between a child who is naturally asleep and one who is beginning to receive excessive opioid. A child who is asleep has a good colour and peripheral perfusion and breathes in an easy unobstructed manner with an S_pO_2 of over 95% while breathing air. A child becoming over sedated may breathe with the mouth hanging open and be partially obstructed. An S_pO_2 of less than 94% is uniform. Sensible and experienced paediatric nurses are usually able to discriminate between these situations and as long as they are prepared to stimulate a child if there is the slightest doubt this system has proved to be very satisfactory in clinical practice at providing early warning of excessive opioid administration.

The incorporation of a score for postoperative nausea and vomiting tends to make doctors and nurses more aware of this distressing symptom and this may encourage early treatment, if required, as well as assessment of the efficacy of the antiemetic treatment which is given.

Regular checks on the performance of the infusion pump or patient-controlled analgesia machine to ensure that appropriate doses of opioid are being administered and that the machine has not failed or over delivered are necessary. Although problems of this kind are rare, they are potentially disastrous. When patient-controlled analgesia is used, if there is a significant difference between the numbers of demands for analgesia which are made and the number which are successful this may suggest that the machine is being used inappropriately and that a further explanation of correct use is required or that the settings are inadequate for the patient.

Further Aspects of Patient-Controlled Analgesia

A further aspect of patient-controlled analgesia which may be useful on occasion is its ability to act as a pain measuring device. This is a return to the original concept which led to patient-controlled analgesia and allows studies of various analgesic techniques in an ethical manner with patient-controlled analgesia being used by patients to make up for any deficiency in the analgesic regimen(s) under investigation (rescue analgesia). The opioid consumption by patient-controlled analgesia is then used as one indicator of the degree and duration of pain experienced by the subject and the efficacy or otherwise of the interventions under investigation.

A variation on patient-controlled analgesia which has been used successfully in children is nurse-controlled analgesia [Lloyd-Thomas and Howard, 1994]. With this technique a modest infusion of morphine sulphate ($10\text{-}20\text{ micrograms kg}^{-1}\text{ hour}^{-1}$) is supplemented by additional boluses ($10\text{-}20\text{ micrograms kg}^{-1}$) given at the discretion of the nurse caring for the child with a lockout interval of 15-30 minutes and a four hourly maximum dose. This offers the advantages of avoiding a generous fixed infusion rate which may be excessive in some subjects while offering a basal level of analgesia which can be supplemented as required and titrated to the needs of the child. It also has the advantage of requiring an obligatory assessment of the patient by the nurse before any opioid boluses are administered. When used appropriately nurse-controlled analgesia appears to be a very effective and safe form of postoperative analgesia which combines some of the better features of both fixed infusions and patient-controlled analgesia in children unable to use patient-controlled analgesia properly.

The use of a patient-controlled analgesia machine by parents to administer analgesia to children has been described [Broadman et al, 1990]. This was a

small series and some parents found the process very stressful. The technique has not become popular and most workers consider that the emotional involvement of parents and their lack of training make them unsuitable to reliably make impartial decisions about the administration of potent analgesics to their child.

Patient-controlled analgesia has been used for chronic and terminal pain in adults [Citron, 1986; Kerr, 1988] and children [Mowbray and Gaukroger, 1990] and for terminal care in ambulatory children [Doyle and Morton, 1994].

Proposed Project

In 1992, despite the growing body of experience with patient-controlled analgesia in children, most of the reported experience consisted of series of patients which demonstrated the efficacy of the technique or its superiority to intermittent intramuscular injections. The technique was becoming widely used but there was no published work investigating patient-controlled analgesia to compare the different regimens in use in a scientific manner and there was no evidence to support the superiority of any particular patient-controlled analgesia regimen in children. The work incorporated in this thesis was conceived and carried out with the aim of investigating this area in a series of randomised, controlled studies to determine the efficacy and the incidence of side effects of different regimens. Features of interest were the size of the bolus dose, the place of a background infusion and its magnitude, the place of the subcutaneous route as an alternative to the intravenous route of administration and the treatment of postoperative nausea and vomiting.

In order to allow valid comparisons between groups a standard surgical procedure was used for most of the studies. This was the operation of appendicectomy which provides a good model for the study of postoperative analgesic regimens in children. It provides a standard incision and surgical procedure with a degree of peritoneal irritation which is magnified by the movements of respiration and mobilisation. This ensures that postoperative morphine requirements when self-administered with a patient-controlled analgesia machine are of the order of 20-30 micrograms kg⁻¹ hour⁻¹ which is the same as that seen in many children after more major abdominal and orthopaedic procedures [Brown and Broadman, 1987; Rogers et al, 1988; Broadman et al, 1989; Lawrie et al, 1990].

CHAPTER TWO

Comparison of Patient-Controlled Analgesia with and without a Background Infusion.

Summary

Forty children aged 6-14 years undergoing appendicectomy were randomly allocated to receive one of two patient-controlled analgesia regimens with intravenous morphine sulphate. Group B0 received a bolus dose of 20 micrograms kg^{-1} with a lockout interval of five minutes and no background infusion and Group B20 received a bolus dose of 20 micrograms kg^{-1} with a lockout interval of five minutes and a continuous background infusion of 20 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$. Patients breathed air and oxygen saturation was monitored by continuous pulse oximetry. Scores for pain, nausea and sedation were recorded hourly. Group B20 received significantly more morphine than Group B0. Both groups self-administered similar amounts of morphine using the patient-controlled analgesia machine. There were no significant differences between the pain scores of the two groups. Group B20 suffered more nausea ($p < 0.01$), more over sedation ($p < 0.05$) and more hypoxic episodes ($p < 0.001$) than Group B0. Group B20 had a better sleep pattern than Group B0.

Introduction

Patient-controlled analgesia has been used in children since 1987 [Brown and Broadman, 1987], initially in adolescents and later in selected children as young as five years. The drug used most commonly has been morphine sulphate with a bolus dose of 10-25 micrograms kg^{-1} and a lockout interval of 5-15 minutes. A continuous background infusion has been used in some studies.

The addition of a background infusion to patient-controlled analgesia may improve the quality of analgesia provided by maintaining plasma concentrations of opioid and in particular by limiting the reduction in plasma concentrations which occurs during sleep [Kay, 1981]. However, a fixed infusion may reduce the inherent safety of patient-controlled analgesia by continuing to deliver opioid to a patient who has adequate analgesia and is at risk of overdose if further opioid is administered [Owen, Mathers and Rowley, 1988]. The use of a background infusion may also result in larger amounts of opioid being administered and an increase in the incidence of opioid-induced side effects [McKenzie, 1988].

This study was carried out to assess the effect on postoperative analgesia, sedation, ventilatory frequency, arterial oxygen saturation ($\text{S}_\text{p}\text{O}_2$), nausea and vomiting and sleeping pattern of adding a background infusion to a patient-controlled analgesia regimen with morphine sulphate in children.

Patients and Methods

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained for each subject. Forty children aged 6-14 years undergoing appendicectomy were studied. Patients were visited preoperatively when the principles of using patient-controlled analgesia were explained to the child and parents and the patients were taught how to use the trigger of the patient-controlled analgesia machine. Patients were not recruited if they had received preoperative analgesia.

All patients received a standard general anaesthetic which consisted of a rapid sequence induction with thiopentone $5-7 \text{ mg kg}^{-1}$ and suxamethonium 1 mg kg^{-1} . The trachea was intubated and the lungs ventilated with isoflurane 0.5-2% with 70% nitrous oxide in oxygen. Neuromuscular blockade was maintained with vecuronium 0.1 mg kg^{-1} . Morphine sulphate 0.1 mg kg^{-1} was given during the procedure. At the end of surgery, residual neuromuscular blockade was antagonised with neostigmine and glycopyrrolate in appropriate doses. In the recovery area, patients were made pain free with increments of $50 \text{ micrograms kg}^{-1}$ of morphine sulphate as required.

Before patients left the recovery area the patient-controlled analgesia machine (Graseby PCAS or Graseby 3300) was connected. The solution used consisted of morphine sulphate 1 mg kg^{-1} diluted in 50 ml of normal saline to give a concentration of $20 \text{ micrograms kg}^{-1} \text{ ml}^{-1}$. The patient-controlled analgesia machine was attached to the side arm of a Cardiff one way valve connected to the intravenous cannula. The settings used were a bolus dose of 1 ml ($20 \text{ micrograms kg}^{-1}$) with a lockout interval of five minutes. Patients were randomly allocated (by means of a computer generated list) to receive either no background infusion or a background infusion of 1 ml hour^{-1} ($20 \text{ micrograms kg}^{-1} \text{ hour}^{-1}$) of morphine sulphate.

After operation patients breathed air and a monitoring regimen described previously [Morton, 1993] was used. The arterial oxygen saturation was monitored continuously and there were hourly recordings of respiratory rate, a pain score, a sedation score, a nausea score, the number of demands made and the volume of solution infused. Oximeter readings were considered valid if artefact was excluded and the reading was consistent over several minutes with a good pulse signal displayed on the oximeter screen. A hypoxic episode was defined as an SpO₂ of less than 94%.

Pain was recorded using a four-point self reporting score which has been validated previously [Maunuksela et al, 1987]: 0 = no pain, 1 = not really sore, 2 = quite sore, 3 = very sore. Subjects who were asleep were allocated a score of 0.

Sedation was scored using a four point scale: 0 = eyes open spontaneously, 1 = eyes open to speech (also used for subjects who were considered to be asleep), 2 = eyes open when shaken, 3 = unrouseable. Over sedation was defined as a score of 2 or 3.

Nausea and vomiting was scored on a four point scale: 0 = none, 1 = nausea only, 2 = vomited once in the past hour, 3 = vomited more than once in the last hour.

Patient-controlled analgesia was discontinued when there was a consistent decline in use and patients were able to take oral analgesics.

Statistical analysis was with Student's t test for parametric data (ages and weights), the Mann-Whitney U test for non-parametric data (opioid consumption, duration of P.C.A. and pain scores) and the Chi squared test for categorical data (comparisons of events between groups).

Results

The two groups were similar with regard to demographic data and surgical details (Table 2.1).

Table 2.1. Demographic data (mean (SD)) and times of operation in Groups B0 and B20.

	Group B0	Group B20
Sex (M:F)	11:9	12:8
Age/years	9.6 (1.7)	10.2 (1.4)
Weight/kg	33.5 (12.6)	32.8 (9.3)
Time of operation:		
06:00-22:00	11	13
22:00-06:00	9	7

The total morphine consumption in Group B20 was significantly greater ($p < 0.01$) than in Group B0. There was no significant difference in the amounts of morphine self-administered by the two groups (Table 2.2).

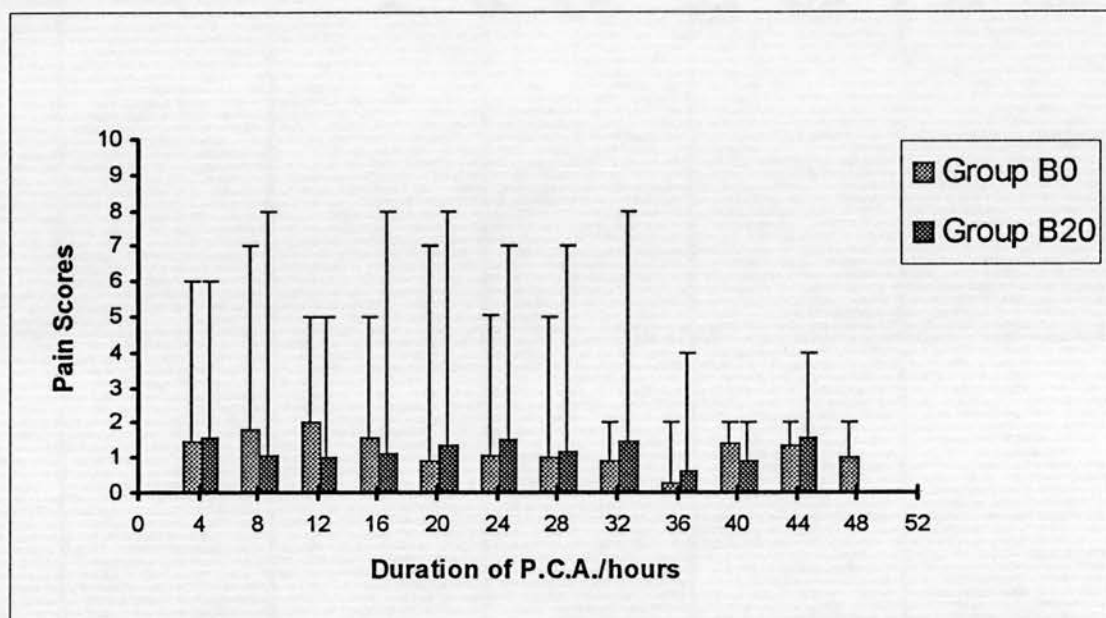
Table 2.2. Details of morphine consumption (Median (Range)) in Groups B0 and B20.

	Group B0	Group B20
Duration of P.C.A./hours	35.5 (15-65)	36.0 (24-51)
Total morphine use/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	1000 (380-1800) 26.5 (11.1-66.7)	1260 (860-2900)** 45 (21-65.9)**
Self-administered morphine/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	1000 (380-1800) 26.5 (11.1-66.7)	650 (20-2020) 25 (1-45.9)
Background infusion/ micrograms kg ⁻¹		720 (200-1020)

** Significant difference between groups (p < 0.01).

For each patient the hourly pain scores during each four hourly interval after operation were summed and a median total pain score in each Group for each four hourly interval calculated. Comparisons of these scores showed no significant differences between the groups during any period (Figure 2.1).

Figure 2.1. Comparison of Pain Scores (Median (Range)) in Groups B0 and B20.



There were significantly more hypoxic episodes ($S_pO_2 < 94\%$) in Group B20 (143 episodes) than in Group B0 (94 episodes) ($p < 0.001$). The lowest values for S_pO_2 recorded ranged from 83-95% (mean 91%) in Group B20 and from 88-94% (mean 92%) in Group B0.

A respiratory rate of less than 10 breaths minute^{-1} was noticed on four occasions in the same patient in Group B20. The S_pO_2 values on these occasions were 96%, 93%, 97% and 90% respectively. The slowest respiratory rate in the two groups ranged from 7-18 breaths minute^{-1} (mean 16 breaths minute^{-1}) in Group B20 and from 12-20 breaths minute^{-1} (mean 17 breaths minute^{-1}) in Group B0.

The occurrence of sedation scores of 2 or 3 was compared. There were no recordings of 3 in either group, but there was a significantly greater number

of occasions when a score of 2 occurred in Group B20 (13 episodes) than in Group B0 (4 episodes) ($p < 0.05$).

There was a significantly higher incidence of vomiting in Group B20 (37 episodes) than in Group B0 (15 episodes) ($p < 0.01$). Antiemetics were given to one patient in Group B20.

The amount of time that patients in the two groups spent asleep was compared separately for the periods from 22:00-06:00 (night) and from 06:00-22:00 (day). Patients in Group B20 spent significantly more time asleep at night than those in Group B0 ($p < 0.001$). There was no difference between the groups in the time spent asleep during the day (Table 2.3). Similar numbers of patients in both groups underwent surgery during the day and at night. The effect of timing of operation on subsequent postoperative sleep pattern can, therefore, be expected to be similar in both groups.

Table 2.3. Comparison of the amount of time in hours spent asleep at night and during the day in Groups B0 and B20.

	Group B0	Group B20
Night		
Asleep	154	198***
Awake	162	105
Day		
Asleep	71	78
Awake	352	361

*** Significant difference ($p < 0.001$) between Groups.

The analgesia provided in both groups was generally very good with only 119 scores of 2 (= quite sore) and 3 (= very sore) from a total of 1521 observation (59 of 759 observations in Group B0 and 60 of 762 observations in Group B20).

One child in Group B20 had the infusion discontinued because of a persistently low S_pO_2 when asleep, although the respiratory rate was always greater than 14 breaths minute⁻¹.

Discussion

This study found that the use of a background infusion of morphine sulphate of 20 micrograms kg⁻¹ hour⁻¹ in a patient-controlled analgesia regimen for children undergoing lower abdominal surgery produced a significant increase in morphine consumption without improving pain relief and a significant increase in the incidence of side effects (respiratory depression, over sedation and nausea and vomiting). Patients in Group B20 did, however, spend more time asleep at night than those in Group B0.

The use of a concurrent background infusion with patient-controlled analgesia in adults is an area of debate in the literature. A background infusion has been shown to improve pain relief in two studies [Sinatra et al, 1989; McKenzie, Rudy and Tantisira, 1990]. In one of these [McKenzie, Rudy and Tantisira, 1990], the use of a background infusion after hysterectomy not only improved analgesia but was associated with an improved sleep pattern and increased patient satisfaction without an increase in the incidence of opioid related side effects such as nausea and vomiting. Significant respiratory depression was not observed. Other studies have shown no benefit when a background infusion was added to a patient-

controlled analgesia regimen [Owen et al, 1989, Wu and Purcell, 1990; Parker, Holtmann and White, 1992]. In these studies morphine consumption was increased with no improvement in analgesia. Two studies [Sinatra et al, 1989; Parker, Holtmann and White, 1992] found an increase in opioid induced side effects other than respiratory depression (based on the intermittent recording of respiratory rate) with a background infusion although arterial oxygen saturation was not monitored. The size of background infusion used in these adult studies varied from 0.6 mg hour⁻¹ to 1.5 mg hour⁻¹ of morphine sulphate (pethidine 10 mg hour⁻¹ in one) which is equivalent to 10-20 micrograms kg⁻¹ hour⁻¹.

In paediatric practice, two studies have compared patient-controlled analgesia with and without a background infusion. Berde used a background infusion of morphine sulphate of 15 micrograms kg⁻¹ hour⁻¹ [Berde et al, 1991]. In this study the P.C.A. only group received bolus doses of 25 micrograms kg⁻¹ and the background infusion group received bolus doses of 18 micrograms kg⁻¹. The lockout time was ten minutes in both groups. There were no differences in morphine consumption, sedation, nausea or vomiting between the groups. Respiratory depression (assessed by intermittent recording of respiratory rate) was not noted in any patient. The background infusion group had lower pain scores than the P.C.A. only group. Pain was assessed using patient and nurse visual analogue scales whereas the study described here used a patient self-report score and this may account for the different results of the two studies which are otherwise similar. Another study in children [Skues et al, 1993] found that a background infusion of 20 micrograms kg⁻¹ hour⁻¹ of morphine sulphate increased opioid consumption but did not improve analgesia. It was, however, associated with a better sleep pattern than patient-controlled analgesia only with no increase in the incidence of side effects.

This is the first study to have shown an increased incidence of respiratory depression in patients receiving a background infusion compared with those receiving P.C.A. only. Respiratory depression has been considered to be a risk associated with the addition of a background infusion to patient-controlled analgesia, but has not previously been shown to occur. The reason for this is probably that previous studies comparing patient-controlled analgesia with and without a background infusion have relied on the intermittent recording of respiratory rate as an indicator of respiratory depression. This has been shown to be a late and insensitive monitor of respiratory depression [Catley et al, 1985; Kluger et al, 1992]. Arterial oxygen saturation while breathing air is a more sensitive monitor of adequate ventilation [Hutton and Clutton-Brock, 1993] and it has been suggested that continuous pulse oximetry should be routine in children receiving systemic opioids [Morton and Gillespie, 1991]. An S_pO_2 of 94% corresponds to a PaO_2 of about 10 kPa in healthy patients and indicates mild hypoxia with a reduced reserve should further respiratory depression occur. In the absence of other causes of hypoxaemia this indicates a degree of hypoventilation which may be the result of opioid administration or of pain. Studies which have relied on the intermittent recording of respiratory rate as an indicator of respiratory depression and have concluded that a background infusion does not produce respiratory depression may be falsely reassuring. This emphasises the need for continuous monitoring and repeated assessments by experienced staff.

The use of patient-controlled analgesia in adults is associated with an incidence of respiratory depression. This may occur in up to 40% of patients breathing air after upper abdominal surgery [Wheatley et al, 1992]. Patients using patient-controlled analgesia after lower abdominal surgery have been shown to be more likely to suffer episodes of mild hypoxaemia than patients receiving intramuscular or extradural morphine [Browse, Powar and Cohen, 1988]. Other studies have shown no difference in the incidence of

hypoxaemia in adults using patient-controlled analgesia and those receiving intramuscular morphine [Wheatley et al, 1992].

Despite the discouraging results of this study, there was a strong clinical impression that subjects receiving a background infusion were more comfortable than those with patient-controlled analgesia only and that the use of a background infusion made the postoperative 36-48 hours less unpleasant. This clinical impression together with the definite advantage in terms of postoperative sleep pattern and data from other studies suggesting benefits from the use of a background infusion encouraged further investigation of the use of background infusions in children using patient-controlled analgesia.

CHAPTER THREE

Patient-Controlled Analgesia with Different Background Infusions.

Summary

Forty five children aged 6-14 years undergoing appendicectomy received one of three analgesic regimens using patient-controlled analgesia with morphine sulphate: no background infusion (Group B0); a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ (Group B4); or a background infusion of 10 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ (Group B10). The bolus dose was 20 micrograms kg^{-1} and the lockout interval 5 minutes in all three groups. Total morphine consumption was greater in Group B10 than in Group B0 ($p < 0.01$) and Group B4 ($p < 0.05$). There was no significant difference in the morphine consumption of Groups B4 and B0. All three Groups self-administered similar amounts of morphine and there were no significant differences in pain scores or the incidence of over sedation. Group B4 suffered fewer episodes of hypoxaemia than Group B0 ($p < 0.05$) and Group B10 ($p < 0.01$). Group B10 suffered more nausea and vomiting than Groups B0 ($p < 0.01$) and B4 ($p < 0.01$) but there was no significant difference in the incidence of nausea and vomiting between Groups B0 and B4. Groups B4 and B10 spent more time asleep at night than Group B0 ($p < 0.05$). There was no significant difference between the groups in the amount of time spent asleep during the day. The inclusion of a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate in a patient-controlled analgesia regimen for children did not increase the incidence of side effects and was associated with less hypoxaemia and a better sleep pattern than no background infusion.

Introduction

Following the previous study, it was decided to investigate two smaller background infusions for use with patient-controlled analgesia in children to determine if any benefits from these could be provided without the unacceptable increase in the incidence of side effects caused by a background infusion of 20 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate.

Patients and Methods

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained for each subject. Forty five children aged 6-14 years undergoing appendicectomy were recruited. Subjects were visited before operation when the principles of using patient-controlled analgesia were explained to the child and parents and the patient was taught to use the trigger of the patient-controlled analgesia pump. Patients were not recruited if they had received preoperative analgesia.

All patients received a standard general anaesthetic which comprised a rapid sequence induction with thiopentone 5-7 mg kg^{-1} and suxamethonium 1 mg kg^{-1} . The trachea was intubated and the lungs ventilated with isoflurane 0.5-2% with 70% nitrous oxide in oxygen. Neuromuscular blockade was maintained with vecuronium 0.1 mg kg^{-1} . Morphine sulphate 0.1 mg kg^{-1} was given during the procedure. At the end of surgery, neuromuscular blockade was antagonised with neostigmine and glycopyrrolate in appropriate doses. In the recovery area, patients were made pain free with increments of 50 micrograms kg^{-1} of morphine sulphate if required.

Before patients left the recovery area, the patient-controlled analgesia pump (Graseby PCAS or Graseby 3300) was set up. The solution used consisted of morphine sulphate 1 mg kg^{-1} diluted in 50 ml of normal saline to give a concentration of $20 \text{ micrograms kg}^{-1} \text{ ml}^{-1}$. The syringe was attached to the side arm of a Cardiff anti-reflux valve connected to the intravenous cannula. Patients were randomly allocated (by means of a computer generated list) to receive one of three different regimens. Group B0 received bolus doses of $20 \text{ micrograms kg}^{-1}$ with a lockout interval of 5 minutes and no background infusion; Group B4 received bolus dose of $20 \text{ micrograms kg}^{-1}$ with a lockout interval of 5 minutes and a background infusion of $4 \text{ micrograms kg}^{-1} \text{ hour}^{-1}$ (0.2 ml hour^{-1}); Group B10 received bolus doses of $20 \text{ micrograms kg}^{-1}$ with a lockout interval of 5 minutes and a background infusion of $10 \text{ micrograms kg}^{-1} \text{ hour}^{-1}$ (0.5 ml hour^{-1}).

Postoperatively patients breathed air and the monitoring protocol described previously [Morton, 1993] was used. There was continuous monitoring of arterial oxygen saturation and hourly recordings of respiratory rate and scores for pain, sedation and nausea and vomiting. The number of demands made and the volume of solution used were also recorded hourly. Oximeter readings were regarded as accurate if they lasted for several minutes, artefact had been excluded and there was a good pulse signal displayed on the monitor. A hypoxic episode was defined as an SpO_2 of less than 94%.

P.C.A. was discontinued when there was a consistent decline in use and patients were able to take oral analgesics.

Statistical analysis was performed as in the previous study.

Results

The Groups were similar with regard to demographic characteristics and timing of operation (Table 3.1).

Table 3.1. Demographic data (Mean (SD)) and timing of operation.

	Group B0	Group B4	Group B10
Sex (M:F)	7:8	8:7	10:5
Age/years	10.5 (1.6)	10.4 (1.9)	10.3 (1.3)
Weight/kg	35.5 (9.0)	35.9 (6.8)	40.0 (10.7)
Time of operation			
06:00-22:00	10	9	10
22:00-06:00	5	6	5

Patients in all three Groups self-administered similar amounts of morphine using the patient-controlled analgesia machine. Total morphine consumption was significantly greater in Group B10 than in Group B0 ($p < 0.01$) and Group B4 ($p < 0.05$). There was no significant difference between the total morphine consumption in Groups B0 and B4 (Table 3.2).

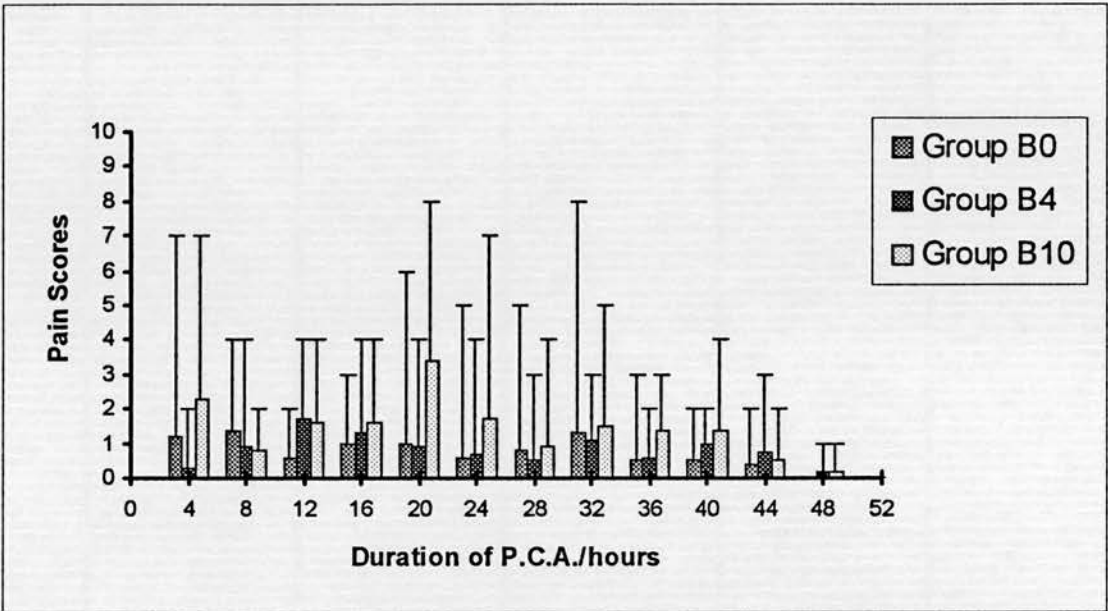
Table 3.2. Details of patient-controlled analgesia use and morphine consumption (Median (Range)) in Groups B0, B4 and B10.

	Group B0	Group B4	Group B10
Duration of P.C.A. use/hours	37 (31-49)	45 (25-61)	42 (26-79)
Total morphine micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	760 (360-1700) 20 (11-42)	964 (440-2060)* 22 (15-46)*	1450 (600-2690)** 31 (17-73)**
Self-administered morphine micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	760 (360-1700) 20 (11-42)	760 (340-1880) 18 (11-42)	920 (240-2300) 21 (7-63)

* Significant difference between groups B4 and B10 ($p < 0.05$); ** Significant difference between Groups B0 and B10 ($p < 0.01$).

For each patient the hourly pain scores during each four hourly interval after operation were summed and a median pain score in each Group for each four hourly interval calculated. Comparisons of these scores showed no significant differences between the groups at any period (Figure 3.1).

Figure 3.1. Comparison of Pain Scores (Median (Range)) in Groups B0, B4 and B10.



Group B10 had significantly more hypoxic episodes (159 episodes) than Group B0 (78 episodes) ($p < 0.01$) and Group B4 (56 episodes) ($p < 0.05$). Group B0 had significantly more hypoxic episodes (78 episodes) than Group B4 (56 episodes) ($p < 0.05$). The lowest S_pO_2 values in the three Groups were 86-95% (mean 91%) in Group B0, 86-95% (mean 92%) in Group B4 and 86-95% (mean 90%) in Group B10.

The slowest respiratory rates recorded in the three groups were 12-18 breaths minute⁻¹ in Group B0, 12-20 breaths minute⁻¹ in Group B4 and 14-18 breaths minute⁻¹ in Group B10.

Group B10 suffered significantly more vomiting (60 episodes) than Groups B0 (20 episodes) ($p < 0.01$) and B4 (22 episodes) ($p < 0.01$). There was no significant difference in the incidence of nausea and vomiting between Groups B0 and B4. Antiemetics were given to one patient in Group B10.

A sedation score of 3 was not recorded in any patient. A sedation score of 2 occurred on 22 occasions in Group B0, 19 occasions in Group B4 and on 21 occasions in Group B10 (not significant).

The amount of time spent asleep was compared in the three groups by analysing the periods from 22:00 to 06:00 (night) and from 06:00 to 22:00 (day) separately. Groups B4 and B10 spent significantly more time asleep at night than patients in Group B0 ($p < 0.05$). There was no significant difference between Groups B4 and B10 in the amount of time spent asleep at night and no significant differences between the Groups in the amount of time spent asleep during the day (Table 3.3). Similar numbers of patients in each group underwent operation at night and during the day.

Table 3.3. Comparison of the amount of time in hours spent asleep at night and during the day in Groups B0, B4 and B10.

	Group B0	Group B4	Group B10
Night			
Asleep	142*	178	217
Awake	78	61	68
Day			
Asleep	85	92	86
Awake	272	308	311

* Significant difference ($p < 0.05$) compared with Groups B4 and B10.

Three patients in Group B10 had the background infusion discontinued because of persistent over sedation.

Discussion

This study showed that the use of a background infusion of 4 micrograms $\text{kg}^{-1} \text{hour}^{-1}$ of morphine sulphate in a patient-controlled analgesia regimen for children after lower abdominal surgery caused no increase in side effects compared with no background infusion and was associated with less hypoxaemia and a better sleep pattern than patient-controlled analgesia only. A background infusion of morphine of 10 micrograms $\text{kg}^{-1} \text{hour}^{-1}$ was also associated with an improved sleep pattern but was accompanied by a significant increase in the incidence of hypoxaemia and postoperative nausea and vomiting. Unlike a background infusion of 20 micrograms $\text{kg}^{-1} \text{hour}^{-1}$, these smaller background infusions were not accompanied by an increase in the incidence of over sedation.

The reason why a background infusion of 4 micrograms $\text{kg}^{-1} \text{hour}^{-1}$ produces less hypoxaemia than a patient-controlled analgesia regimen without a background infusion is likely to be that the infusion produced better analgesia and improved ventilation. This suggests that the method of assessing pain used in this study (patient self-report) is relatively insensitive. A specific assessment of pain on moving or coughing may have revealed differences in analgesia between Groups B0, B4 and B10. We have previously noted that periods of hypoxaemia often correspond with high pain scores [Morton, 1993].

In adult studies, the use of a background infusion has been shown to improve pain relief in two studies [Sinatra et al, 1989; McKenzie et al, 1990], but not in others [Owen et al, 1989; Wu and Purcell, 1990; Parker, Holtmann and White, 1992]. The studies which found no benefit from a background infusion did not assess pain during movement. In contrast, one of the studies which did find improved analgesia with a background infusion [Sinatra et

al, 1989] did assess pain during movement. The other study [McKenzie et al, 1990] did not make clear if pain was assessed at rest or during movement. Two studies [Sinatra et al, 1989; Parker, Holtmann and White, 1992] found an increase in opioid induced side effects other than respiratory depression such as nausea and pruritis with a background infusion although arterial oxygen saturation was not monitored.

The results of this study indicated that the use of a background infusion with patient-controlled analgesia in children produced benefits in terms of postoperative sleep pattern and hypoxaemia without an increase in side effects. It strongly suggested that a background infusion improved pain control and that the method of scoring or assessing pain used was insufficiently sensitive to discriminate between analgesic regimens.

CHAPTER FOUR

Comparison of Patient-Controlled Analgesia with and without a Background Infusion of Four micrograms kg⁻¹ hour⁻¹ of Morphine Sulphate.

Summary

Forty children aged 6-14 years undergoing appendicectomy received one of two analgesic regimens using patient-controlled analgesia with morphine sulphate: no background infusion (Group B0) or a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ (Group B4). The bolus dose was 20 micrograms kg^{-1} and the lockout interval 5 minutes in both groups. Both Groups self-administered similar amounts of morphine sulphate. There was no difference in the pain scores between the Groups when this was assessed at rest but Group B4 had significantly lower pain scores when pain was assessed during a specified movement ($p < 0.01$). Group B4 suffered fewer episodes of hypoxaemia than Group B0 ($p < 0.001$). There was no significant difference in the incidence of nausea and vomiting or of over sedation between Groups B0 and B4. Group B4 spent more time asleep at night than Group B0 ($p < 0.05$). There was no significant difference between the groups in the amount of time spent asleep during the day. The inclusion of a background infusion of morphine sulphate of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ in a patient-controlled analgesia regimen for children improved analgesia and was associated with less hypoxaemia and a better sleep pattern than no background infusion. The background infusion did not increase the incidence of side effects.

Introduction

Following the previous study and the demonstration that a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate was superior to no background infusion in reducing the incidence of postoperative hypoxaemia, the two regimens were compared in a similar way but with pain scoring being carried out after a specified movement. The reason why differences between the pain scores of the groups in the previous two studies had not been found was presumed to be because pain was assessed at rest and that this was an inadequately sensitive discriminator between regimens. A background infusion of 10 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ was not included in this study because it was felt that although it may improve analgesia, the increase in side effects seen when it was used made it unacceptable for routine future use.

Patients and Methods

The study was approved by the hospital Ethics Committee. Forty children aged 6-14 years undergoing appendicectomy were recruited. Subjects were visited before operation when the principles of using patient-controlled analgesia were explained to the child and parents and the patient was taught to use the trigger of the patient-controlled analgesia pump. Patients were not recruited if they had received preoperative analgesia.

All patients received a standard general anaesthetic which comprised a rapid sequence induction with thiopentone 5-7 mg kg^{-1} and suxamethonium 1 mg kg^{-1} . The trachea was intubated and the lungs ventilated with isoflurane 0.5-2% with 70% nitrous oxide in oxygen. Neuromuscular blockade was maintained with vecuronium 0.1 mg kg^{-1} . Morphine sulphate

0.1 mg kg⁻¹ was given during the procedure. At the end of surgery, neuromuscular blockade was antagonised with neostigmine and glycopyrrolate in appropriate doses. In the recovery area, patients were made pain free with increments of morphine sulphate 50 micrograms kg⁻¹ if required.

Before patients left the recovery area, the patient-controlled analgesia pump (Graseby PCAS or Graseby 3300) was set up. The solution used consisted of morphine sulphate 1 mg kg⁻¹ diluted in 50 ml of normal saline to give a concentration of 20 micrograms kg⁻¹ ml⁻¹. The syringe was attached to the side arm of a Cardiff anti-reflux valve connected to the intravenous cannula. Patients were randomly allocated (by means of a computer generated list) to receive one of two different regimens. Group B0 received bolus doses of 20 micrograms kg⁻¹ with a lockout interval of 5 minutes and no background infusion; Group B4 received bolus dose of 20 micrograms kg⁻¹ with a lockout interval of 5 minutes and a background infusion of 4 micrograms kg⁻¹ hour⁻¹ (0.2 ml hour⁻¹).

Postoperatively patients breathed air and the monitoring protocol described previously [Morton, 1993] was used. There was continuous monitoring of arterial oxygen saturation and hourly recordings of respiratory rate and scores for pain, sedation and nausea and vomiting. Scores for pain were noted both at rest and immediately after a specified movement (a deep breath followed by a cough). The number of demands made and the volume of solution used were also recorded hourly. Oximeter readings were regarded as accurate if they lasted for several minutes, artefact had been excluded and there was a good pulse signal displayed on the monitor. A hypoxic episode was defined as an S_pO₂ of less than 94%.

P.C.A. was discontinued when there was a consistent decline in use and patients were able to take oral analgesics.



Statistical analysis was performed as in the previous studies.

Results

The Groups were similar with regard to demographic characteristics and timing of operation (Table 4.1).

Table 4.1. Demographic data (Mean (SD)) and timing of operation.

	Group B0	Group B4
Sex (M:F)	11:9	12:8
Age/years	10.1 (1.8)	10.3 (1.9)
Weight/kg	35.7 (11.9)	35.3 (10.3)
Time of operation		
06:00-22:00	12	10
22:00-06:00	8	10

One patient in Group B0 and three in Group B4 received a bolus of morphine 50 micrograms kg^{-1} in the recovery area. These boluses are not included in the figures for postoperative consumption of morphine. Patients in both Groups self-administered similar amounts of morphine using the trigger of the patient-controlled analgesia machine. Total morphine consumption was significantly greater in Group B4 than in Group B0 ($p < 0.05$) (Table 4.2).

Table 4.2. Details of patient-controlled analgesia use and morphine consumption (Median (Range)) in Groups B0 and B4.

	Group B0	Group B4
Duration of P.C.A. use/hours	40 (33-51)	42 (36-56)
Total morphine consumption/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	790(360-1700) 22 (11-66)	1024 (428-2440)* 28.4 (10.8-61)*
Self-administered morphine/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	790 (360-1700) 22 (11-66)	880 (280-2280) 24.4 (6.8-57)

* Significant difference between groups ($p < 0.05$).

For each patient the hourly pain scores during each four hourly period after the start of patient-controlled analgesia were added and a median score obtained for each of these periods in each Group. There were no significant differences between the scores of the two groups at any of these times when assessments were made at rest but the scores in Group B4 were significantly lower than those in Group B0 ($p < 0.01$) when assessments were performed during movement. The mean four hourly totals for patients in the two groups at rest are shown in Figure 4.1 and those during movement in Figure 4.2.

Figure 4.1. Comparison of Pain Scores (Median (Range)) in Groups B0 and B4 at Rest.

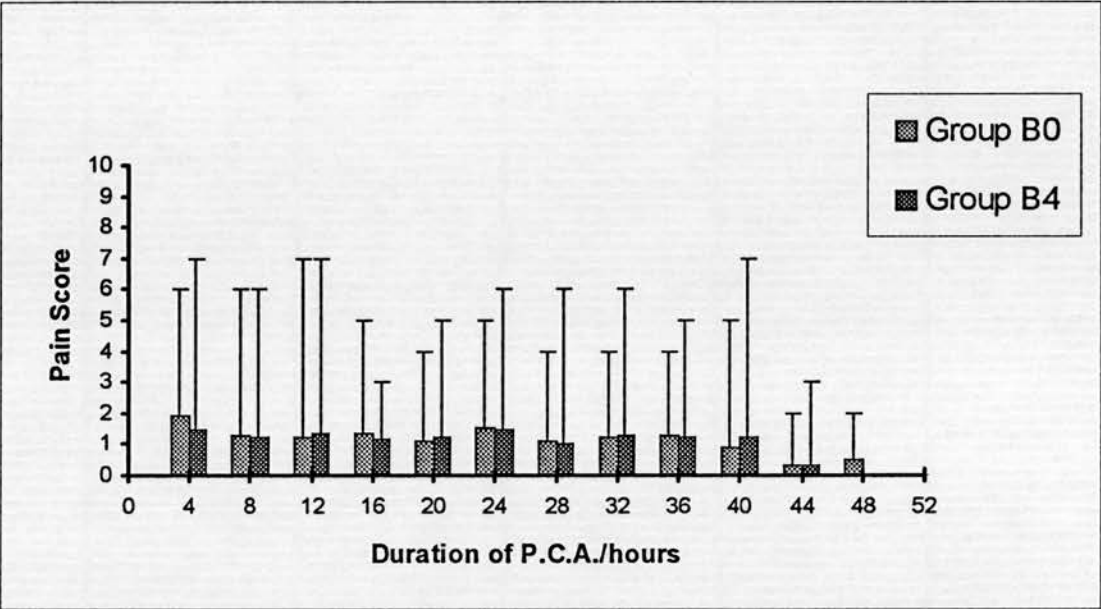
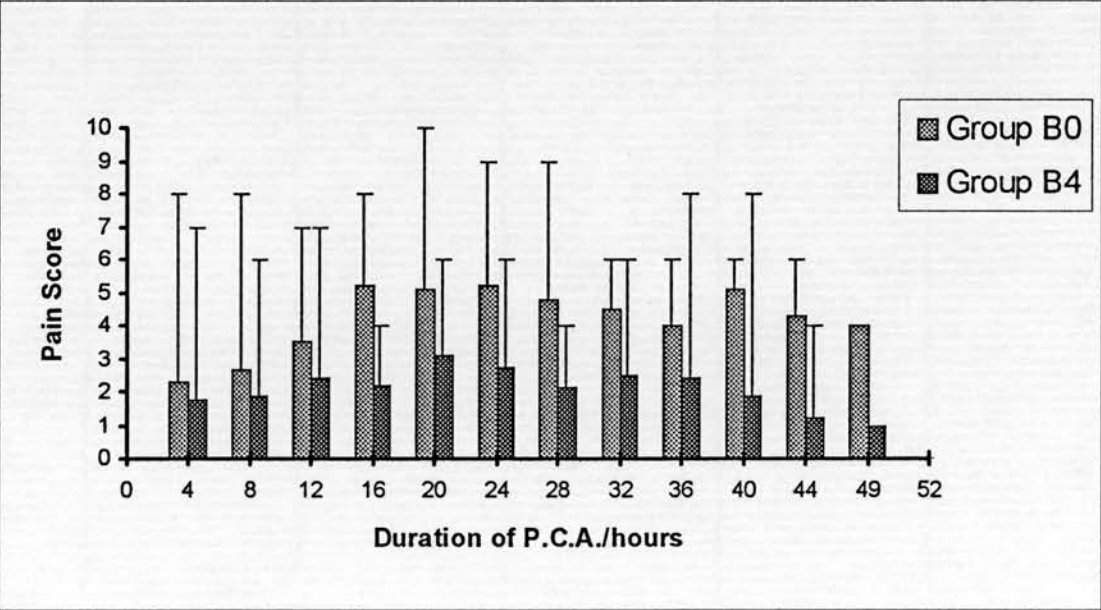


Figure 4.2. Comparison of Pain Scores (Median (Range)) in Groups B0 and B4 during Movement.



Group B0 had significantly more ($p < 0.01$) hypoxic episodes (100 episodes) than Group B4 (63 episodes). The lowest S_pO_2 values in the two Groups were 86-95% (mean 91%) in Group B0 and 86-95% (mean 92%) in Group B4. The slowest respiratory rate recorded was 12 breaths minute^{-1} in both Groups.

There was no significant difference in the incidence of nausea and vomiting between Groups B0 and B4. A sedation score of three was not recorded in any patient. There was no difference between the groups in the incidence of sedation scores of 2.

The amount of time spent asleep was compared in the two groups by analysing the periods from 22:00 to 06:00 (night) and from 06:00 to 22:00 (day) separately. Group B4 spent significantly more time asleep at night than patients in Group B0 ($p < 0.01$). There was no significant difference between the Groups in the amount of time spent asleep during the day (Table 4.3). Similar numbers of patients in each group underwent operation at night and during the day.

Table 4.3. Comparison of the amount of time in hours spent asleep at night and during the day in Groups B0 and B4.

	Group B0	Group B4
Night		
Asleep	187	243**
Awake	125	81
Day		
Asleep	116	112
Awake	366	398

** Significant difference between groups ($p < 0.01$).

Discussion

This study confirmed that the use of a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate in a patient-controlled analgesia regimen for children after lower abdominal surgery caused no increase in side effects compared with no background infusion and was associated with less hypoxaemia and a better sleep pattern than patient-controlled analgesia only. It also demonstrated better analgesia with a background infusion than with patient-controlled analgesia only. The improved analgesia provided by the background infusion was only demonstrated when pain was assessed during a movement and this emphasises the importance of performing pain assessments in this way [Kehlet, 1994].

The lower incidence of hypoxic episodes in Group B4 may be explained as a consequence of better analgesia resulting in less hypoventilation caused by pain. In patients breathing air, pulse oximetry is a sensitive monitor of adequate ventilation [Hutton and Clutton-Brock, 1993]. Consideration of the ideal alveolar gas equation shows that with an inspired oxygen concentration of 21%, a small increase in alveolar carbon dioxide tension produces a decrease in alveolar oxygen tension sufficient to reduce the arterial oxygen saturation from a normal value of 97-100%. An arterial oxygen saturation of 94% corresponds to an arterial oxygen tension of about 10 kPa and is associated with mild hypoventilation in healthy patients. This is a non-specific monitor of ventilation and differentiation between the possible causes (excess opioid, pain and a problem with gas exchange) requires examination of the patient with assessment of opioid consumption, degree of analgesia and level of sedation. A patient who is hypoxic because of excess opioid will be sedated while a patient in pain will be alert and unwilling to take a deep breath and cough. The possibility of other causes of impaired gas exchange should always be borne in mind. The fact that there was no

difference between the groups in the incidence of over sedation suggests that the morphine consumption in Group B4 was not excessive and that the hypoxia seen in Group B0 was a consequence of hypoventilation due to pain rather than excessive opioid consumption. In summary, it appears that the inclusion of a small background infusion of about 4 micrograms $\text{kg}^{-1} \text{hour}^{-1}$ in a patient-controlled analgesia regimen for children produces better analgesia and a more natural sleep pattern after surgery without causing an increase in the incidence of opioid induced side effects. A consequence of this improved analgesia is a reduction in the incidence of hypoxic episodes caused by hypoventilation in patients receiving a background infusion.

CHAPTER FIVE

Comparison of Different Bolus Doses of Morphine Sulphate for Patient-Controlled Analgesia.

Summary

Forty children aged 6-14 years undergoing appendicectomy were randomly allocated to receive one of two patient-controlled analgesia regimens with morphine sulphate. Group B10 received bolus doses of 10 micrograms kg^{-1} and Group B20 received bolus doses of 20 micrograms kg^{-1} . In both groups there was a lockout interval of five minutes and a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$. Group B20 self-administered significantly more morphine ($p < 0.01$) than Group B10. There was no difference between the pain scores of the groups at rest. Group B20 had significantly lower pain scores ($p < 0.05$) during movement than Group B10. Group B10 suffered significantly more ($p < 0.01$) hypoxaemic episodes than Group B20. There were no differences between the groups in the incidence of vomiting, over sedation or time spent asleep at night.

Introduction

Regimens described for patient-controlled analgesia in children have used bolus doses ranging from 10 to 25 micrograms kg^{-1} of morphine sulphate but there have been no comparative studies of different bolus doses in children in terms of efficacy and side effects. This study was carried out to compare two common bolus doses of morphine sulphate of 10 micrograms kg^{-1} and 20 micrograms kg^{-1} in a patient-controlled analgesia regimen for children. Features of interest were efficacy, morphine consumption and the incidence of side effects. The patient-controlled analgesia regimen used included a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ which was shown in the previous study to be superior to a patient-controlled analgesia regimen without a background infusion. The study included an assessment of pain during movement described in the previous study to improve sensitivity and to aid discrimination between the regimens.

Patients and Methods

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained for all subjects. Forty children aged 6-14 years undergoing appendicectomy were recruited. Subjects were visited preoperatively when the principles of using patient-controlled analgesia were explained to the child and parents. Patients were taught to use the trigger of the patient-controlled analgesia machine during this visit. Patients were not recruited if they had received preoperative analgesia.

All patients received a standard general anesthetic which consisted of a rapid sequence induction with thiopentone 5-7 mg kg^{-1} and suxamethonium

1 mg kg⁻¹. The trachea was intubated and the lungs ventilated with isoflurane 0.5-2% with nitrous oxide 70% in oxygen. Neuromuscular blockade was maintained with vecuronium 0.1 mg kg⁻¹. Morphine sulphate 0.1 mg kg⁻¹ was given during the procedure. At the end of surgery neuromuscular blockade was reversed with neostigmine 50 micrograms kg⁻¹ and glycopyrrolate 10 micrograms kg⁻¹. In the recovery area patients were titrated to comfort with boluses of morphine sulphate 50 micrograms kg⁻¹ if required.

Before patients left the recovery area the P.C.A. machine (Graseby PCAS or Graseby 3300) was set up. The solution used consisted of morphine sulphate 1 mg kg⁻¹ diluted in 50 ml of normal saline to give a concentration of 20 micrograms kg⁻¹ ml⁻¹. The P.C.A. machine was connected to the side arm of an anti-reflux valve attached to the intravenous cannula. Patients were randomly allocated (by means of a computer generated list) to receive one of two different patient-controlled analgesia regimens. Group B10 received bolus doses of morphine of 10 micrograms kg⁻¹ (0.5 ml) with a lockout interval of 5 minutes and a background infusion of 4 micrograms kg⁻¹ hour⁻¹ (0.2 ml hour⁻¹); Group B20 received bolus doses of 20 micrograms kg⁻¹ (1 ml) with a lockout interval of 5 minutes and a background infusion of 4 micrograms kg⁻¹ hour⁻¹.

After operation patients breathed air. The monitoring protocol described previously [Morton, 1993] was used with assessments of pain at rest and during movement as described in the previous study.

Patient-controlled analgesia was discontinued when there was a consistent decline in use and patients were able to take oral analgesics.

Statistical analysis was as described for the previous studies.

Results

The two groups were similar demographically (Table 5.1) and with respect to the timing of surgery.

Table 5.1. Demographic data (Mean (SD)) and timing of surgery in Groups B10 and B20.

	Group B10	Group B20
Sex (M:F)	12:8	10:10
Age/years	10.7 (1.9)	10.3 (1.4)
Weight/kg	33.9 (7.2)	35.1 (9.9)
Time of surgery		
06:00-22:00	12	10
22:00-06:00	8	10

Patients in Group B20 self-administered significantly more morphine than those in Group B10 ($p < 0.01$). There was no significant difference between the groups in the duration of patient-controlled analgesia use or the percentage of unsuccessful demands (demands made during the lockout period) for analgesia (Table 5.2).

Table 5.2. Details of P.C.A. use and morphine consumption (Median (Range)) in Groups B10 and B20.

	Group B10	Group B20
Duration of P.C.A. use/hours	41 (32-60)	41 (29-59)
Morphine consumption/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	505 (70-850)** 14.7 (5.9-29.9)**	850 (260-2940) 29.5 (11.2-61)
Self-administered by P.C.A./ micrograms kg ⁻¹ hour ⁻¹	10.7 (1.9-25.9)**	25.5 (7.2-57)
Successful demands/%	73 (35-94)	81 (42-98)

** Significant difference ($p < 0.01$) between groups.

For each patient the hourly pain scores during each four hourly interval after operation were summed and a median total pain score in each Group for each four hourly interval calculated. There were no significant differences between the groups at rest at any time except for the period 16-20 hours postoperatively when the difference just reached significance at the 5% level (Figure 5.1). Pain scores during movement in Group B20 were significantly lower ($p < 0.05$) than those in Group B10 during each four hour period except for that 44-48 hours after operation (Figure 5.2). At 44-48 hours after operation no patient in Group B20 complained of pain at rest although some did have pain on movement.

Figure 5.1. Comparison of Pain Scores (Median (Range)) in Groups B10 and B20 at Rest.

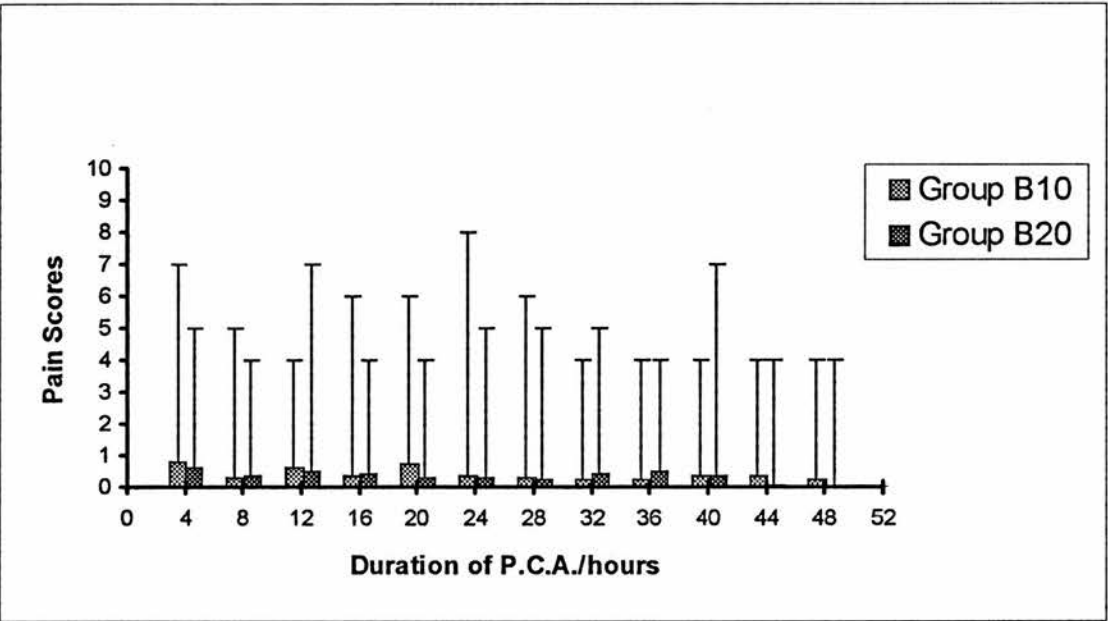
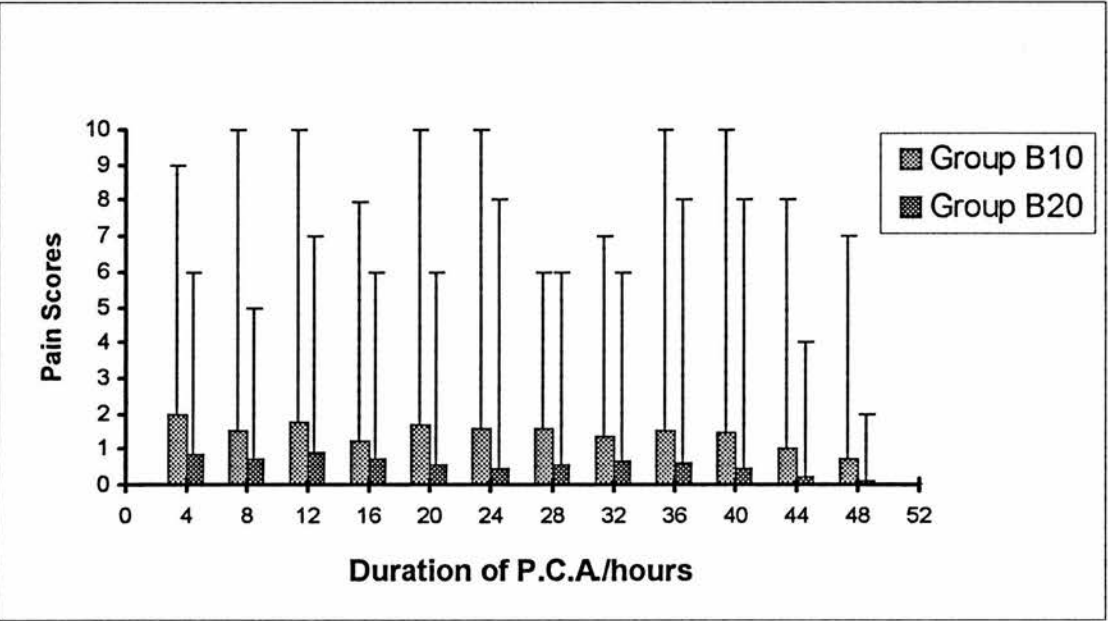


Figure 5.2. Comparison of Pain Scores (Median (Range)) in Groups B10 and B20 during Movement.



There were significantly more S_pO₂ recording of less than 94% in Group B10 (92 episodes) than in Group B20 (61 episodes) ($p < 0.01$).

There was no significant difference in the incidence of vomiting in the two groups after operation (six patients in Group B10 and three patients in Group B20).

There were no episodes of over sedation in any patient in either group.

The amount of time that patients spent asleep was assessed by comparing the periods from 22:00-06:00 (night) and from 06:00-2200 (day) separately. There was no significant difference between the groups during either of these periods (Table 5.3).

Table 5.3. Comparison of amount of time in hours spent asleep in Groups B10 and B20.

	Group B10	Group B20
Night		
Asleep	207	209
Awake	140	134
Day		
Asleep	95	89
Awake	417	407

Discussion

This study showed that when patient-controlled analgesia is used in children a bolus dose of morphine of 10 micrograms kg^{-1} is associated with higher pain scores and more hypoxic episodes than a bolus dose of 20 micrograms kg^{-1} . There was no difference between the groups in the incidence of other opioid-induced side effects, sleep pattern or the percentage of unsuccessful demands for analgesia.

The optimal bolus dose for use with patient-controlled analgesia has been defined as the minimum dose which produces adequate analgesia consistently without causing subjective or objective side effects [Owen et al, 1989]. An inadequate bolus dose tends to result in inadequate analgesia, while too large a bolus may cause excessive side effects. Ideally, patients should not be required to make too frequent demands in order to obtain adequate analgesia.

These findings are in agreement with those of adult studies where inadequate bolus doses were associated with increased pain scores [Keeri-Santo, 1979; Owen et al, 1990]. In these studies, patients did not use the patient-controlled analgesia machine to achieve adequate analgesia despite the fact that there was a facility to administer more analgesic. This suggests that patients do not always use patient-controlled analgesia to titrate analgesic drugs to a minimum effective analgesic concentration. The time since the previous analgesic demand and the expected benefit from a demand in terms of analgesia appear to be important factors in the frequency of demands made by patients.

The finding of an increased incidence of hypoxic episodes in Group B10 presumably reflects hypoventilation as a consequence of pain causing

restriction of abdominal movement in this group. The association of hypoxaemia with high pain scores has been noticed previously [Morton, 1993]. This association may be a consequence of pain leading to inhibition of ventilation or of a relative overdose of opioid. Since there was no excess of over sedation in Group B20, these results suggest that the higher incidence of hypoxaemia in Group B10 was a result of inadequate analgesia causing hypoventilation.

The marked disparity between the sensitivity of scoring pain at rest and during movement at discriminating between the two regimens confirms that pain scoring at rest is inadequate and only assessments on movement should be used to guide analgesic therapy.

CHAPTER SIX

Comparison of Intravenous and Subcutaneous Infusions of Morphine Sulphate for the Treatment of Postoperative Pain.

Summary

The intravenous and subcutaneous routes of administration were compared for infusions of morphine sulphate in children undergoing abdominal surgery. Forty children aged 4-11 years underwent balanced anaesthesia with epidural blockade and received morphine up to 30 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ postoperatively. There were no differences between the groups in opioid consumption, pain scores or the incidence of opioid-induced side effects. The subcutaneous route appears to be as effective and safe as the intravenous route for the administration of opioid infusions in children undergoing elective surgery.

Introduction

The use of intravenous opioid infusions to treat postoperative pain in children is a common and effective analgesic technique which has been used for many years [Bray, 1983; Pounder and Steward, 1992]. The technique requires a second dedicated intravenous cannula for opioid administration in addition to one for intravenous fluids and drugs. Alternatively, the same cannula may be used for both fluids and opioid administration but in order to avoid the risk of reflux of opioid into the intravenous tubing with the possibility of a subsequent uncontrolled bolus, an anti-reflux valve must be placed at the junction of the intravenous cannula and the fluid giving set. The option of a second intravenous cannula is not always available particularly in infants and anti-reflux valves are expensive and make the infusion site bulky and difficult to nurse.

An alternative route of administration for opioid infusions which does not have these disadvantages is the subcutaneous route. This has been used extensively in terminal [Nahata, Miser and Reuning, 1984] and chronic pain [Kerr et al, 1988] and has also been described for acute pain in adults [Goudie et al, 1985; Hindsholm et al, 1993]. The subcutaneous route has been used for the administration boluses of opioid in children [Wandless and Lavies, 1989] and the efficacy of subcutaneous infusions of morphine has been demonstrated [McNicol, 1993]. For this technique to become widespread and accepted it must be shown to have equal efficacy to the traditional intravenous route with the same or a lower incidence of side effects. The intravenous and subcutaneous routes of administration have not been compared in children and this study was designed to compare them in children undergoing abdominal surgery in terms of efficacy and the incidence of side effects.

Patients and Methods

The study was approved by the hospital Ethics Committee. Forty children aged 4-11 years undergoing abdominal surgery with combined general anaesthesia and epidural blockade were studied. Exclusion criteria included contraindications to epidural blockade and significant hepatic or renal impairment. Patients were premedicated with EMLA cream at least one hour preoperatively and anaesthesia was induced with propofol $3-4 \text{ mg kg}^{-1}$ and vecuronium 0.1 mg kg^{-1} . Following endotracheal intubation, the lungs were ventilated with isoflurane 0.5-2% with 70% nitrous oxide in oxygen. Patients were then turned into the lateral position and a single epidural injection of 0.8 ml kg^{-1} of 0.25% bupivacaine (2 mg kg^{-1}) (maximum 20 ml) given. At the end of surgery neuromuscular blockade was reversed with neostigmine and glycopyrrolate in appropriate doses and the trachea extubated.

Patients were randomised to receive either an intravenous or a subcutaneous infusion of morphine sulphate postoperatively. In the intravenous group (Group IV) a second 22G cannula was sited intravenously on the same side as the cannula used for induction. In the subcutaneous group (Group SC) a 24G cannula was sited subcutaneously over the deltoid muscle on the same side as the intravenous cannula. Morphine infusions were started in the recovery area.

In Group IV the solution used consisted of morphine sulphate 1 mg kg^{-1} diluted in 50 ml of 0.9% saline to give a concentration of $20 \text{ micrograms kg}^{-1} \text{ ml}^{-1}$. The intravenous infusion was commenced at a rate of 1 ml hour^{-1} ($20 \text{ micrograms kg}^{-1} \text{ hour}^{-1}$). In Group SC the solution used consisted of 1 mg kg^{-1} of morphine sulphate diluted in 20 ml of 0.9% saline to give a concentration of $50 \text{ micrograms kg}^{-1} \text{ ml}^{-1}$. This was commenced at 0.4 ml hour^{-1} ($20 \text{ micrograms kg}^{-1} \text{ hour}^{-1}$).

Postoperatively patients breathed air and the monitoring protocol described previously [Morton, 1993] was used with assessments of pain at rest and during movement. Morphine sulphate was infused at a maximum rate of 30 micrograms kg⁻¹ hour⁻¹ and further bolus doses of morphine sulphate 50 micrograms kg⁻¹ were available if required.

Infusions were discontinued when there was a consistent decline in opioid requirements and patients were able to take oral analgesics.

Statistical analysis was performed as in the previous studies.

Results

The two groups were similar with respect to demographic characteristics, surgical procedures and the duration of surgery (Table 6.1).

Table 6.1. Demographic data (Mean (SD)) and surgical characteristics of Groups IV and SC.

	Group IV	Group SC
Male:Female	9:11	12:8
Age/years	8.4 (2.2)	8.8 (2.2)
Weight/kg	27.1 (6.3)	25.3 (5.8)
Gastrointestinal/Genitourinary	9:11	11:9

The duration of infusion analgesia and the total opioid consumption were similar in the two groups (Table 6.2).

Table 6.2. Details of opioid consumption and duration of infusion (Median (Range)) in Groups IV and SC.

	Group IV	Group SC
Duration/hours	40.5 (19-75)	36.5 (24-56)
Morphine consumption		
micrograms kg ⁻¹	740 (260-1450)	700 (420-1240)
micrograms kg ⁻¹ hour ⁻¹	19.3 (9.4-24.2)	20.7 (11.8-28.6)

For each patient the hourly pain scores during each four hourly interval after operation were summed and a median total pain score in each Group for each four hourly interval calculated. Comparisons of these scores showed no significant differences between the groups during any period (Figure 6.1). There were no significant differences between the groups at any point. Four children in Group IV and three children in Group SC received one supplementary bolus of morphine for inadequate analgesia at the maximum infusion rate.

Figure 6.1. Comparison of Pain Scores (Median (Range)) in Groups IV and SC at Rest.

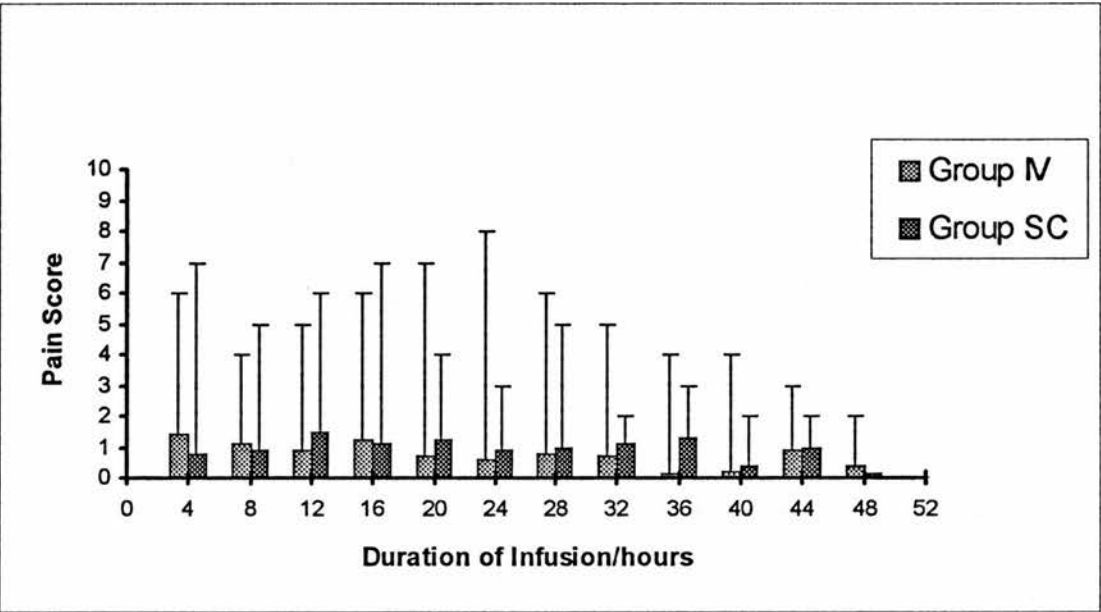
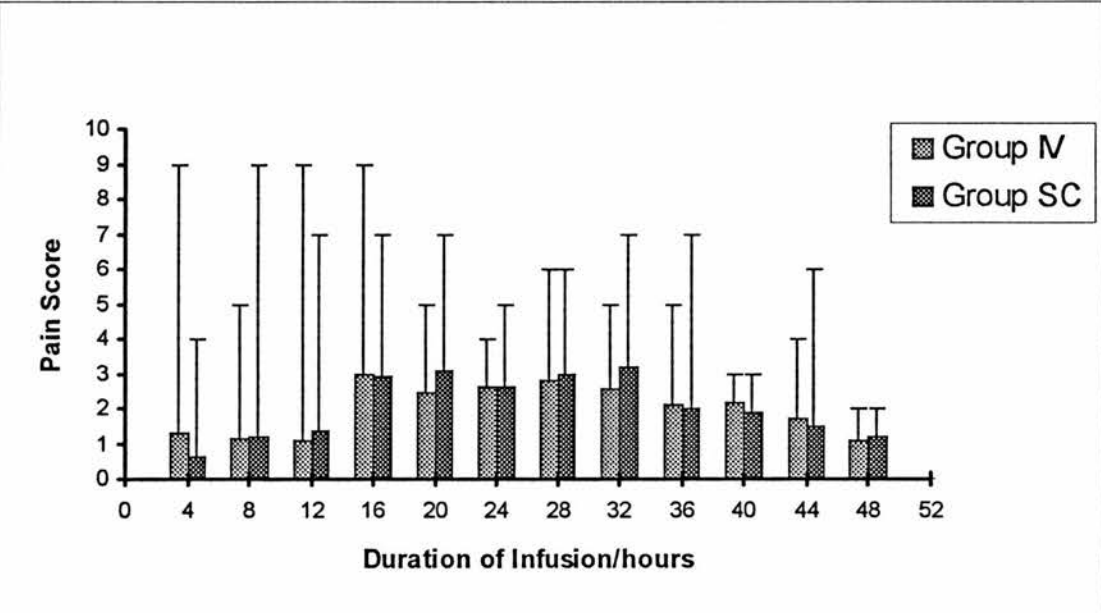


Figure 6.2. Comparison of Pain Scores (Median (Range)) in Groups IV and SC during movement.



There were no differences between the Groups in the incidence of vomiting, over sedation or in the number of hypoxic episodes (Table 6.3).

Table 6.3. Episodes of hypoxia, over sedation and postoperative vomiting in Groups IV and SC.

	Group IV	Group SC
Hypoxia	32	24
Over sedation	3	5
Vomiting	39	29

Six cannulae in Group IV and one cannula in Group SC needed to be replaced during the opioid infusion.

Discussion

This study demonstrated that the subcutaneous route of administration is as effective as the intravenous route for the infusion of opioids in children after elective surgery. Although subcutaneous administration has been shown to provide analgesia [McNicol, 1993] in children it has not previously been shown to be as effective as the intravenous route. The fact that equivalent analgesia can be provided by this route with similar doses of morphine and no increase in the incidence of side effects suggests that this technique will prove to be a useful in this group of patients. The advantages of avoiding the

need for a dedicated intravenous cannula or for an anti-reflux valve are considerable in small children. Use of the subcutaneous route for opioid infusions is likely to reduce the practical difficulties associated with the provision of this form of analgesia in children.

It should be remembered that the subjects in this study were elective normovolaemic patients with normal cardiac output. The subcutaneous route would be contraindicated in patients with or at risk of developing poor peripheral perfusion where there would be a risk of accumulation of opioid at the infusion site with poor analgesia and subsequent absorption of this depot to give the equivalent of a large uncontrolled bolus of opioid [Wolf et al, 1995].

CHAPTER SEVEN

Comparison of the Intravenous and Subcutaneous Routes of Administration for Patient- Controlled Analgesia.

Summary

Sixty children aged 6-14 years undergoing appendicectomy were randomly allocated to receive one of two P.C.A. regimens with morphine sulphate. Group IV received intravenous patient-controlled analgesia with a bolus dose of 20 micrograms kg^{-1} and a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ while Group SC received patient-controlled analgesia by the subcutaneous route with a bolus dose of 20 micrograms kg^{-1} and a background infusion of 5 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$. In both groups there was a lockout interval of 5 minutes. Group SC self-administered significantly less morphine ($p < 0.05$) and had a significantly greater ($p < 0.01$) percentage of valid demands for analgesia than Group IV. There were no differences between the pain scores of the two groups at rest or during movement. Group IV suffered significantly ($p < 0.01$) more hypoxic episodes than Group SC. There were no differences between the groups in the incidence of over sedation or postoperative nausea and vomiting. Subcutaneous patient-controlled analgesia appears to be as effective and safe as intravenous patient-controlled analgesia. By giving patients feedback on the occurrence of valid demands for analgesia subcutaneous patient-controlled analgesia may produce more effective and appropriate use of the machine.

Introduction

Following the demonstration that the subcutaneous route of administration is as effective as the intravenous route for the administration of opioid infusions in selected children, it was decided to investigate this route for the administration of patient-controlled analgesia. Both groups received a small background infusion which had previously been shown to be superior to a patient-controlled analgesia regimen with no background infusion.

Patients and Methods

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained for each subject. Sixty children aged 6-14 years undergoing appendicectomy were studied. Patients were visited before operation when the principles of using patient-controlled analgesia were explained to the child and parents. Patients were taught to use the trigger of the patient-controlled analgesia machine during this visit. Patients were not studied if they had received analgesia before operation.

All patients received a standard general anaesthetic which comprised a rapid sequence induction with thiopentone 5-7 mg kg⁻¹ and suxamethonium 1 mg kg⁻¹. The trachea was intubated and the lungs ventilated with 0.5-2% isoflurane in 70% nitrous oxide in oxygen. Neuromuscular block was maintained with vecuronium 0.1 mg kg⁻¹. Morphine sulphate 0.1 mg kg⁻¹ was given during the procedure. At the end of surgery neuromuscular block was antagonised with neostigmine and glycopyrrolate in appropriate doses. In

the recovery area patients were titrated to comfort with bolus doses of morphine 50 micrograms kg^{-1} if required.

Before patients left the recovery area the P.C.A. pump (Graseby PCAS or Graseby 3300) was set up. Patients were randomly allocated (by means of a computer generated list) to receive one of two different patient-controlled analgesia regimens. One group received intravenous patient-controlled analgesia (Group IV) and the other group received patient-controlled analgesia by the subcutaneous route (Group SC). In Group IV the solution used consisted of morphine sulphate 1 mg kg^{-1} diluted in 50 ml of normal saline to give a concentration of 20 micrograms $\text{kg}^{-1} \text{ ml}^{-1}$. The syringe was attached to the side arm of a Cardiff one way anti-reflux valve connected to the intravenous cannula. This group received bolus doses of 20 micrograms kg^{-1} (1 ml) with a lockout interval of 5 minutes and a background infusion of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ (0.2 ml hour^{-1}).

In Group SC, a 22G cannula was sited subcutaneously over the deltoid muscle of the same non-dominant arm as the intravenous cannula. This cannula was flushed with 0.5 ml of 0.9% saline and secured with Elastoplast tape. The syringe was attached to this cannula. In Group SC, the solution used consisted of morphine sulphate 1 mg kg^{-1} diluted in 20 ml of normal saline to give a concentration of 50 micrograms $\text{kg}^{-1} \text{ ml}^{-1}$. This group received bolus doses of 20 micrograms kg^{-1} (0.4 ml) with a lockout interval of 5 minutes and a background infusion of 5 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ (0.1 ml hour^{-1}). This background infusion differed slightly from that used in Group IV because it was not possible to give the same background infusion with the dilution of morphine used.

After operation patients breathed air and the monitoring protocol described previously was used [Morton, 1993]. Patients were asked to quantify the delay between pressing the trigger of the patient-controlled analgesia

machine and the onset of analgesia. Patients were also asked about the presence of pain or discomfort at the site of the subcutaneous cannula and its relation to pressing the trigger of the patient-controlled analgesia machine. Patient-controlled analgesia was discontinued when there was a consistent decline in use and patients were able to take oral analgesics. At the discontinuation of subcutaneous patient-controlled analgesia the cannula was removed and the site inspected.

Statistical analysis was performed as in the previous studies.

Results

The two groups were similar with regard to demographic characteristics (Table 7.1).

Table 7.1. Demographic data (Mean (SD)) of patients in Groups IV and SC.

	Group IV	Group SC
Sex (M:F)	17:13	14:16
Age/years	10.7 (1.9)	10.9 (1.6)
Weight/kg	39.2 (11.4)	36.6 (8.9)

Patients in Group IV self-administered significantly more morphine than those in Group SC ($p < 0.05$). Group SC had a significantly greater percentage of valid demands than Group IV ($P < 0.01$) (Table 7.2).

Table 7.2. Details of patient-controlled analgesia use and morphine consumption (Median (Range)) in Groups IV and SC.

	Group IV	Group SC
Duration of P.C.A./hours	46 (33-80)	42 (21-80)
Total morphine consumption/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	1330 (476-3880) 28.6 (16.3-59.7)	960 (400-3250)* 25.3 (6.5-67.3)*
Self-administered morphine/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	1140 (600-3620) 24.6 (12.3-55.7)	730 (220-2960)* 20.3 (1.5-62.3)*
% Valid demands	75 (23-100)	92 (68-100)**

* Significant difference between groups ($p < 0.05$); ** Significant difference between groups ($p < 0.01$).

Pain scores were compared by calculating the median total pain score (at rest and during movement) during each four hour period after operation and comparing the groups during each of these periods. Figure 7.1 shows the pain scores in the two groups at rest and Figure 7.2 shows the scores in the groups during movement. There were no significant differences between the groups at any of these times.

Figure 7.1. Comparison of Pain Scores (Median (Range)) in Groups IV and SC at Rest.

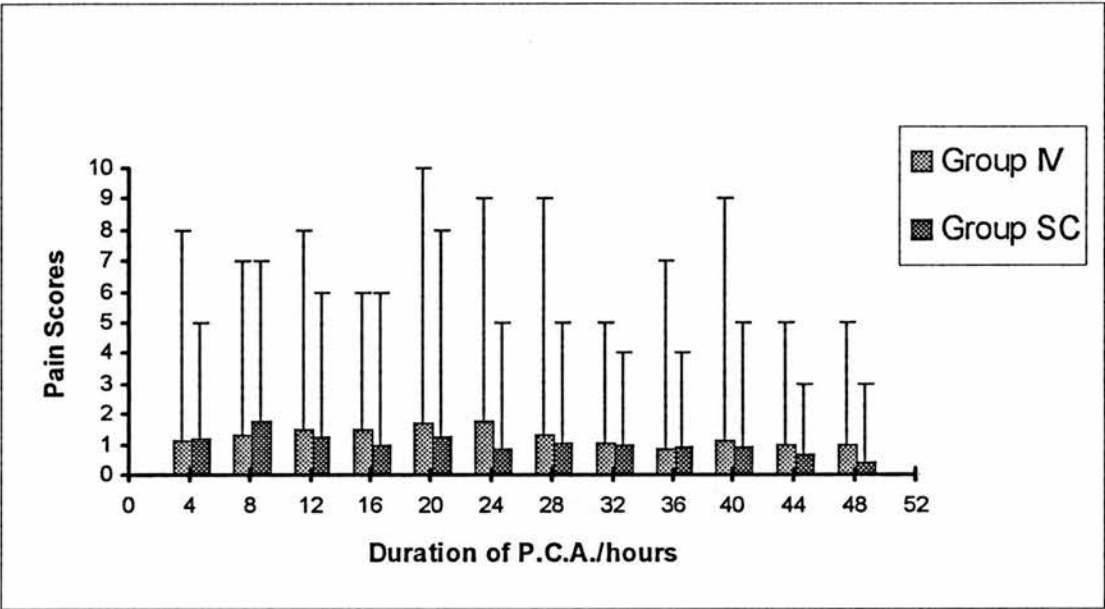
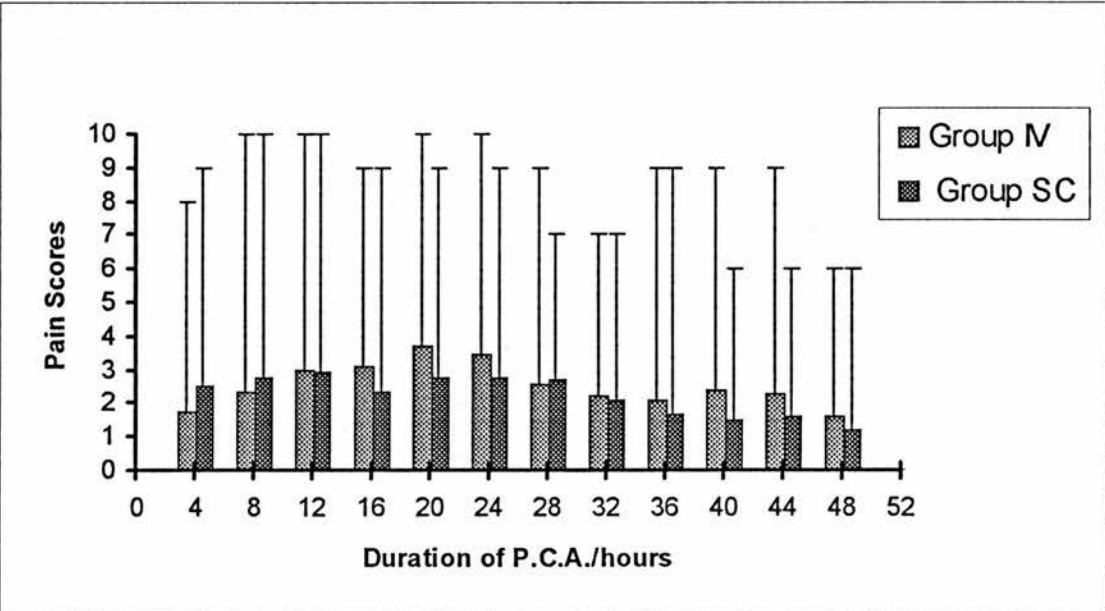


Figure 7.2. Comparison of Pain Scores (Median (Range)) in Groups IV and SC during Movement.



There were significantly more S_pO_2 readings of less than 94% in Group IV than in Group SC ($p < 0.01$) (Table 3). The lowest values recorded were 85% in Group IV and 87% in Group SC.

There were no significant differences between the groups in the incidence of postoperative nausea and vomiting (PONV) or of over sedation (Table 7.3). There were no sedation scores of 3 in any patient.

Table 7.3. Episodes of hypoxia, over sedation and postoperative vomiting in Groups IV and SC.

	Group IV	Group SC
Hypoxia	193	123 **
Vomiting	95	65
Over sedation	10	8

** Significant difference between groups ($p < 0.01$).

Twenty eight patients in Group SC were aware of bolus infusions shortly after making a demand. Five patients in Group SC complained of pain at the cannulation site during bolus dose infusion. In all of these five patients, bolus doses stopped being painful after several hours of patient-controlled analgesia use. Four patients in Group IV were able to feel bolus dose infusions and no patients in this group complained of pain during bolus dose infusion.

In Group SC, 9 patients had a localised erythematous flare at the site of subcutaneous cannulation which started soon after the commencement of patient-controlled analgesia. In all cases this faded after several hours. In Group SC, there were no problems at the cannulation site after removal of the cannulae.

Discussion

This study has shown that subcutaneous patient-controlled analgesia appears to be as effective and safe for the treatment of postoperative pain as intravenous patient-controlled analgesia. It also suggests that the subcutaneous route for patient-controlled analgesia may have advantages over the intravenous route. There was a lower consumption of morphine in Group SC (in patients undergoing the same procedure) associated with a higher proportion of valid demands for analgesia. This was possibly because of the fact that with subcutaneous patient-controlled analgesia patients were aware of bolus infusions and that the demand for analgesia had been successful. Because of this, patients expected the demand to produce analgesia and tended not to make further invalid demands during the lockout period. The usefulness of a positive feedback mechanism to the patient to indicate that a demand for analgesia has been successful has been noted previously [Johnson and Luscombe, 1992; Owen et al, 1993] and patient-controlled analgesia pumps which produce different sounds in response to valid and invalid demands are being developed. It should be remembered that Group SC received a background infusion of $5 \text{ micrograms kg}^{-1} \text{ hour}^{-1}$ compared with $4 \text{ micrograms kg}^{-1} \text{ hour}^{-1}$ in Group IV and this may have been partly responsible for the reduced requirement for self-administered morphine in Group SC. This would not, however, explain the reduction in

total morphine consumption in Group SC compared with Group IV or the higher percentage of valid demands.

The lower incidence of hypoxic episodes in Group SC may be explained by several possible mechanisms. The lower morphine consumption during subcutaneous patient-controlled analgesia may result in less respiratory depression than would otherwise be the case. Improved analgesia as a consequence of more appropriate analgesic administration in response to pain may have reduced the incidence of hypoventilation caused by pain (although this should have been reflected in differences in the pain scores of the groups). Alternatively, differences in the pharmacokinetics of the two routes of administration may produce lower peak concentrations of morphine if boluses are given subcutaneously rather than intravenously. Limited data concerning the absorption of morphine during intravenous and subcutaneous infusions in adults [Waldmann et al, 1984] and children [Morton et al, 1995; Watson et al, 1995] suggest that both routes are equally effective in normovolaemic patients but there are no data concerning absorption after intermittent bolus dose administration. The fact that there was no difference between the groups in the incidence of over sedation suggests that the morphine consumption in Group IV was not excessive.

Although the subcutaneous route of administration is very satisfactory for infusion analgesia in chronic and terminal pain and also acute pain there is concern that the absorption of bolus doses is so slow as to make it unsuitable for use with patient-controlled analgesia. In this study, this proved not to be the case and in all patients the delay to feeling an analgesic effect after making a demand was in the order of a few minutes. We did not attempt to assess this interval accurately because of difficulties for children judging time accurately during the postoperative period.

In summary, subcutaneous patient-controlled analgesia appears to be as effective and safe as intravenous patient-controlled analgesia and it may offer advantages over the intravenous route by providing feedback on successful demands for analgesia and enhancing appropriate use of the pump. It should be restricted to patients who are normovolaemic and unlikely to suffer impaired cardiac output for any reason.

CHAPTER EIGHT

Prevention of Postoperative Nausea and Vomiting during Patient- Controlled Analgesia with Transdermal Hyoscine.

Summary

Forty children aged 6-14 years undergoing abdominal surgery under general anaesthesia with epidural blockade were studied. Subjects were randomly allocated to receive transdermal hyoscine (loading dose 140 micrograms, followed by 5 micrograms hour⁻¹) or placebo for the duration of postoperative analgesia with patient-controlled analgesia using morphine sulphate. There was a significant ($p < 0.001$) reduction in the incidence of postoperative nausea and vomiting in the treated group compared with the placebo group during the first 48 hours after operation. The treated group also had a significantly increased incidence of sedation ($p < 0.02$) and dry mouth ($p < 0.01$).

Introduction

Postoperative nausea and vomiting occurs (PONV) in up to 80% of patients in many series [Palazzo and Strunin, 1984; Clarke, 1984; Kortilla et al, 1979; Kapur, 1991; Uppington et al, 1986]. The causes include the effects of premedicant drugs, anaesthetic agents, postoperative analgesics (especially opioids), the surgical procedure and the susceptibility of the patient. Postoperative nausea and vomiting appears to be a significant problem in patients who use patient-controlled analgesia for postoperative pain relief [Wheatley et al, 1991]. Postoperative nausea and vomiting is also a significant problem in children using patient-controlled analgesia [Lawrie et al, 1990; Gaukroger et al, 1989; Rodgers et al, 1988; Broadman et al, 1989] and may be very distressing for a number of children who use this form of postoperative analgesia.

Several agents with different modes of action are commonly used to treat postoperative nausea and vomiting, including phenothiazines, butyrophenones, antihistamines, dopamine antagonists and anticholinergics. Children are sensitive to the extrapyramidal effects of some of these drugs [Bateman, 1991].

The anticholinergic agent, hyoscine, has been shown to have an antiemetic effect when given intramuscularly [Dundee et al, 1964; Clark et al, 1965]. There is also a preparation of hyoscine in the form of a plaster for transdermal application (Scopoderm TTS {Ciba}) which contains 1.5 mg of hyoscine. This releases 140 micrograms of hyoscine soon after application followed by 5 micrograms hour⁻¹ for up to 72 hours while the plaster is in place giving an average absorption rate of hyoscine of 500 micrograms in 72 hours. The preparation has been shown to have a significant antiemetic effect in motion sickness [Cronin et al, 1982; Price et al, 1981; van Marion et

al, 1985]. Transdermal application of hyoscine offers potential advantages in the prevention of postoperative nausea and vomiting. It produces steady low plasma levels of hyoscine [Muir and Metcalf, 1983] and avoids the problems of a short half-life, brief duration of action and high peak plasma concentrations which occur after intramuscular injection. In paediatric practice the avoidance of intramuscular injections is a particular advantage.

This study was a prospective, placebo controlled, double blind assessment of the efficacy of transdermal hyoscine in preventing postoperative nausea and vomiting in children using patient-controlled analgesia with morphine sulphate after abdominal surgery.

Patients and Methods

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained for each subject. Forty children aged 6-14 years undergoing abdominal surgery were recruited. Exclusion criteria included inability to operate a patient-controlled analgesia machine, contraindications to epidural analgesia and the use of centrally acting antiemetic drugs within the previous week. Before operation subjects were instructed in the principles and use of patient-controlled analgesia.

A standard anaesthetic technique was used. Premedication consisted of diazepam 0.3 mg kg^{-1} orally 2 hours before operation. Anaesthesia was induced with propofol $3-4 \text{ mg kg}^{-1}$ (plus lignocaine 0.2 mg kg^{-1}) and vecuronium 0.1 mg kg^{-1} . The trachea was intubated and the lungs ventilated with isoflurane 0.5-2% with 70% nitrous oxide in oxygen. The patient was then turned into the lateral position and a 'single shot' epidural injection of 0.25% bupivacaine 0.8 ml kg^{-1} (2 mg kg^{-1}) (maximum 20 ml) given at an

appropriate dermatomal level for the proposed surgery. At the end of surgery neuromuscular blockade was reversed with neostigmine and glycopyrrolate in appropriate doses. Patients were titrated to comfort in the recovery area with boluses of 50 micrograms kg^{-1} of morphine sulphate if required.

Patients were randomly allocated (by means of a computer generated list) to two groups of twenty patients. Group H received a hyoscine patch and Group P received a placebo patch. After induction of anaesthesia and before the start of surgery, patients in Group H had a hyoscine patch applied to the skin in the left postauricular area and this was covered with an Elastoplast dressing. Patients in Group P had the dressing alone applied to the area.

Before patients left the recovery area the P.C.A. machine (Graseby P.C.A.S.) was connected. The solution used consisted of morphine sulphate 1 mg kg^{-1} diluted in 50 ml of normal saline to give a concentration of 20 micrograms $\text{kg}^{-1} \text{ ml}^{-1}$. The syringe was attached to the side arm of a Cardiff anti-reflux valve connected to the intravenous cannula. The patient-controlled analgesia settings used were a bolus dose of 1 ml (20 micrograms kg^{-1}), with a lockout interval of 5 minutes. A background infusion was not used.

After operation patients breathed air and the postoperative monitoring protocol described previously was used [Morton, 1993].

Subjects were questioned on each postoperative day for the presence of dry mouth and blurred vision. All assessments were made by an observer blinded to the treatment groups.

Rectal prochlorperazine was prescribed as an antiemetic if required in both groups. Patient-controlled analgesia was discontinued when there was a consistent decline in use and patients were able to take oral analgesics.

Hyoscine and placebo patches were removed at the time patient-controlled analgesia was discontinued.

Statistical analysis was performed as described for the previous studies.

Results

Patient data are shown in Table 8.1. The two groups were similar in all respects.

Table 8.1. Demographic data (Mean (SD)) and details of procedures in Groups H and P.

	Group H	Group P
Sex (M:F)	6:14	7:13
Age/years	11.1 (2.1)	10.2 (1.8)
Weight/kg	39.5 (13.4)	36.9 (11.9)
Duration of anaesthesia/minutes Median (Range)	95 (65-210)	90 (55-210)
Duration of surgery/minutes Median (Range)	75 (45-175)	65 (35-185)
Procedures		
Genitourinary	12	9
Gastrointestinal	8	11

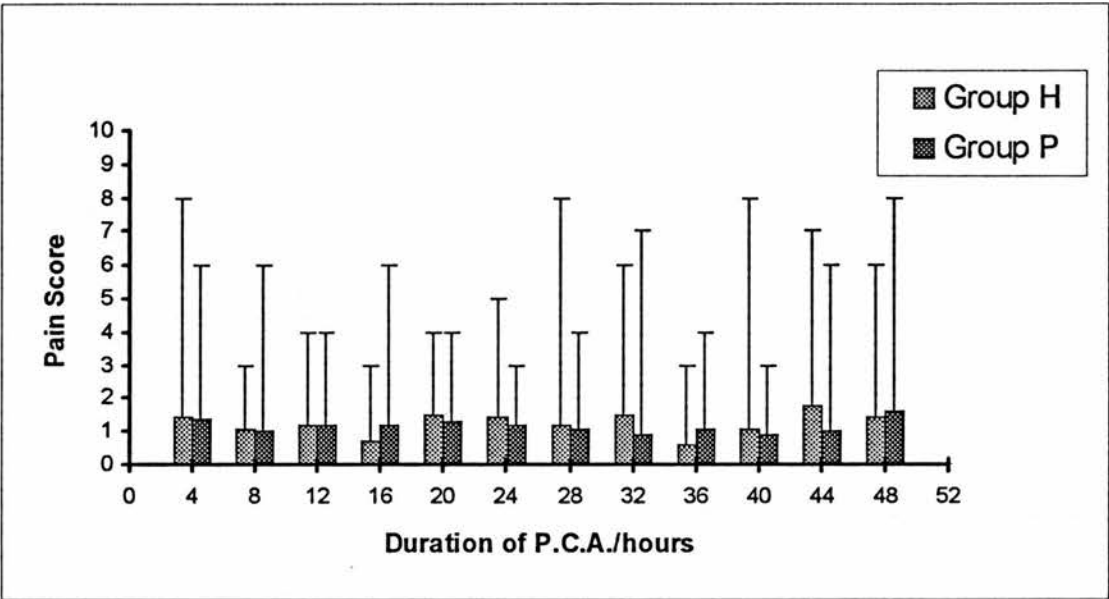
Morphine consumption and the duration of P.C.A. use was similar in the two groups (Table 8.2).

Table 8.2. Details of P.C.A. use and morphine consumption (Median (Range)) in Groups H and P.

	Group H	Group P
Duration of P.C.A. use/hours	48.5 (27-71)	43.5 (32-86)
Morphine consumption/ micrograms kg ⁻¹ micrograms kg ⁻¹ hour ⁻¹	1420 (200-3280) 25.7 (5-59.5)	1280 (340-3020) 22.5 (8-45.1)

Pain scores in the groups were compared by calculating the median total pain score during each four hourly period after the start of P.C.A. in each Group and comparing these for each period. There were no significant differences between the Groups at any time (Figure 8.1).

Figure 8.1. Comparison of Pain Scores (Median (Range)) in Group H and Group P.



There was a significant reduction in the incidence of postoperative nausea and vomiting (defined as a nausea score other than 0) in Group H compared with Group P ($p < 0.001$) during the period of patient-controlled analgesia use (Table 8.3). There was also a significant reduction in the number of patients who complained of postoperative nausea and vomiting at any time in Group H compared with Group P ($p < 0.05$) (Table 8.3). Six patients in Group P and 3 patients in Group H vomited on one or more occasions.

Table 8.3. Comparison of numbers of episodes of PONV and the numbers of patients suffering from PONV in Groups H and P.

	Group H	Group P
Episodes of PONV	29	69***
Patients with PONV at any time	6	14*

* Significant difference between groups ($p < 0.05$); *** Significant difference between groups ($p < 0.001$).

When the antiemetic effect of hyoscine was analysed for each twenty four hour period of use there was a significant ($p < 0.01$) antiemetic effect during the first twenty four hours of use; a significant ($p < 0.01$) effect during the second twenty four hours of use and no significant effect during the third twenty four hour period of use (Table 8.4).

Table 8.4. Comparisons of the antiemetic effects of hyoscine during each twenty four hour period after operation.

Episodes of PONV	Group H	Group P
First 24 hours	20	45**
Second 24 hours	8	17**
Third 24 hours	1	5

** Significant difference between groups ($p < 0.01$).

Two patients in Group P received one dose each of prochlorperazine during patient-controlled analgesia use.

There was no significant difference between the groups in the number of occasions when a S_pO_2 reading of less than 94% occurred (Table 8.5). One patient in Group H was excluded from this analysis because he was receiving supplementary oxygen having suffered a pneumothorax during a nephrectomy. The number of occasions when subjects were considered to be over sedated (sedation score of 2 or 3) was significantly higher in Group H than in Group P ($p < 0.02$). There were no sedation scores of 3 in either group (Table 8.5).

There was no significant difference in the incidence of dry mouth during the first postoperative day but during the second and third postoperative days there was a significantly higher ($p < 0.01$) incidence of this symptom in Group H (Table 8.5). There was no significant difference between the groups in the incidence of blurred vision (Table 8.5).

Table 8.5. Comparison of incidence of side effects in Groups H and P.

	Group H	Group P
Hypoxia	136	117
Over sedation	32	15*
Dry mouth	19	9**
Blurred vision	1	0

* Significant difference between groups ($p < 0.02$); ** Significant difference between groups ($p < 0.01$).

One subject in Group H suffered hallucinations when the hyoscine patch had been in place for 36 hours. This responded quickly to removal of the patch and cleaning the skin at the application site. There were no local reactions at the site of patch application in any patients.

Discussion

This study has demonstrated a significant antiemetic effect of transdermal hyoscine in children using patient-controlled analgesia. Children generally suffer less from postoperative nausea and vomiting than adults when patient-controlled analgesia is used with the incidence varying from 4-35% [Lawrie et al, 1990; Gaukroger et al, 1989; Rodgers et al, 1988; Broadman et al, 1989] compared with 38-82% in adults [Semple et al, 1992; Harris et al, 1991, Wheatley et al, 1991]. Although the majority of nausea scores in our placebo group were 0, this reflects the frequency of observation. More than 67% of patients in Group P suffered postoperative nausea or vomiting.

Other studies on the efficacy of transdermal hyoscine in the prevention of postoperative nausea and vomiting are contradictory. Two studies [Semple et al, 1992; Harris et al, 1991] used transdermal hyoscine in combination with patient-controlled analgesia after intra-abdominal gynaecological surgery without regional blocks. The first of these [Semple et al, 1992] found a reduction in the incidence of postoperative nausea and vomiting immediately and on the third day after operation. The treated group required half the number of supplementary doses of antiemetic as those in the placebo group in this study. Preoperative opioids were omitted and fentanyl was given during operation. The other study [Harris et al, 1991] found a significant antiemetic effect of transdermal hyoscine compared with placebo

and a reduced need for supplementary droperidol in the treated group. There was no opioid premedication and fentanyl was given during surgery.

Two studies [Loper et al, 1989; Kotelko et al, 1989] in patients receiving extradural morphine for postoperative analgesia showed that transdermal hyoscine had a significantly greater antiemetic effect than placebo, with a reduced requirement for supplementary antiemetics. One of these [Loper et al, 1989] studied patients undergoing intra-abdominal gynaecological surgery with general anaesthesia and intraoperative extradural blockade and the other [Kotelko et al, 1989] was in women undergoing Caesarean section under extradural blockade.

Transdermal hyoscine has also been found to be effective in orthopaedic and plastic surgery [Wilkinson et al, 1989]. In contrast, Koski and colleagues found no effect of transdermal hyoscine on the incidence of postoperative nausea and vomiting in female patients although this study was poorly controlled [Koski et al, 1990]. Tigerstedt [Tigerstedt et al, 1988] found transdermal hyoscine was no more effective than placebo or intraoperative droperidol in preventing postoperative nausea and vomiting. This study included a variety of surgical procedures, the hyoscine patches were only applied 50 minutes before surgery, opioid premedication was used in addition to intraoperative fentanyl and postoperative intramuscular opioids were given.

The use of propofol as an induction agent, followed by inhalational agents, causes less postoperative nausea and vomiting than thiopentone [Boysen et al, 1989; Doze et al, 1988; Watcha et al, 1991] and it has been suggested that propofol has antiemetic effects [McCollum et al, 1988]. Avoidance of preoperative opioid premedication and intraoperative opioids is likely to reduce total opioid consumption. An extradural block provides analgesia into

the postoperative period and reduces the requirements for patient-controlled analgesia with morphine in the early postoperative period.

It has been suggested that transdermal hyoscine should be applied several hours before surgery [Rowbotham, 1992] so that therapeutic plasma concentrations are attained perioperatively. It is possible that a more pronounced antiemetic effect would have been found if we had done this rather than apply the patches at the induction of anaesthesia.

The finding of an increased incidence of dry mouth in Group H is in keeping with the results of several previous studies [Harris et al, 1991; Kotelko et al, 1989; Wilkinson et al, 1989; Koski et al, 1990] and is a recognised common side effect of hyoscine. The finding that there was no difference between the groups in the incidence of dry mouth during the first postoperative day probably reflects the high incidence of this in all patients soon after abdominal surgery as a result of preoperative fasting and endotracheal intubation.

Other studies have reported visual disturbances induced by hyoscine used both for travel sickness [Cronin et al, 1982] and for postoperative nausea and vomiting [Uppington et al, 1986; Semple et al, 1992; Koski et al, 1990; Tigerstedt et al, 1988; Bailey et al, 1990]. Our finding of no difference between the groups may reflect a lower incidence of this complication in children or the fact that children are less bothered by this symptom than adults. Psychosis has been reported after transdermal hyoscine [MacEwan et al, 1985; Clissold and Heel, 1985] in children and in adults. It is unusual and easily treated by removing the patch and cleaning the skin.

In summary, transdermal hyoscine has a useful antiemetic effect in children using patient-controlled analgesia after abdominal surgery but its use is associated with an increase in the incidence of over sedation and dry mouth.

Summary

The work described in this thesis is the largest body of published work describing clinical experience with patient-controlled analgesia in children. There are over 11,000 hours of patient use in this series with continuous pulse oximetry while breathing air and hourly assessments of efficacy and the incidence of side effects. In particular, the routine use of continuous pulse oximetry to detect mild hypoventilation is unique.

In terms of efficacy, patient-controlled analgesia has been previously demonstrated to be superior to intermittent bolus dose administration of opioids. The work described here has supported this by demonstrating consistently low pain scores in children undergoing abdominal surgery. It appears that the use of a small background infusion in the region of 4-5 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine sulphate improves the efficacy of patient-controlled analgesia in children by reducing the occurrence of hypoventilation caused by abdominal pain. Rather than increasing the incidence of side effects a background infusion of appropriate size reduces the incidence of hypoxic episodes, has no effect on nausea and vomiting and encourages a natural pattern of sleep with less time spent awake at night than if no background infusion is used. The subcutaneous route of administration is as effective as the intravenous route in appropriately selected patients and has the potential advantages of avoiding the need for a dedicated cannula or an anti-reflux valve. In the event of a technical problem which could cause siphonage of the syringe contents into the patient, use of the subcutaneous route of administration may prevent this happening. This would not be the case if the infusion pump were programmed incorrectly or malfunctioned and infused a large volume of opioid under high pressure.

It should be emphasised that these observations apply only to children undergoing abdominal surgery and that the situation when children use patient-controlled analgesia after orthopaedic or other peripheral surgery

may be different. In these circumstances hypoventilation as a consequence of pain would not be expected to occur and the benefits of a background infusion in reducing the incidence of hypoxic episodes found in this series may not be seen. Since non-abdominal surgery is often associated with a lower incidence of postoperative nausea and vomiting than abdominal surgery, particularly urgent abdominal surgery such as appendicectomy, it may be the case that the use of a small background infusion may increase the incidence of nausea and vomiting after non-abdominal surgery as was seen with the larger background infusion rates. Because of these considerations it is important not to extrapolate the findings of this work too generally.

The most serious potential side effect of opioid based analgesic techniques is ventilatory depression which may occur for one or more of several reasons described in Chapter 1. There were no episodes of life threatening respiratory depression in this series. The lowest S_pO_2 recorded was 83% and the lowest respiratory rate 7 breaths/minute. The majority of episodes of hypoventilation detected by pulse oximetry were mild and associated with S_pO_2 values of over 90%. The very low incidence of more severe hypoxic episodes is reassuring and may indicate that the use of opioid based analgesic techniques in healthy children has a wider margin of safety than in an adult population where a significant incidence of hypoxic episodes can be demonstrated when they are used. There have, however, been cases in the hospital of life threatening episodes of respiratory depression associated with the use of patient-controlled analgesia when parents have ignored instructions and administered morphine to children using the trigger of the patient-controlled analgesia machine. Similar episodes are well described in individual case reports and anecdotal evidence. These together with the other potential causes of an opioid overdose mean that even though the basic concept and technique of patient-controlled analgesia may be safe in children, a monitoring protocol which consistently detects problems at an

early stage must be used in all cases. This should include the use of pulse oximetry while breathing room air although the most important component is the frequent observation of the patient by an appropriately trained nurse with medical support available if required.

The most troublesome side effect of opioids is probably nausea and vomiting. The incidence of this symptom was increased by the use of background infusions of 20 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ and 10 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$ of morphine but not by one of 4 micrograms $\text{kg}^{-1} \text{ hour}^{-1}$. When a specific attempt was made to reduce the incidence of postoperative nausea and vomiting by using transdermal hyoscine in elective patients receiving epidural blockade this was successful but was judged to cause an unacceptable degree of sedation. Because of this limitation the use of transdermal hyoscine has not become common in the hospital since it interferes with a valuable monitor of excessive opioid administration.

Pruritis is described as a common side effect in patients receiving morphine. This was not formally looked for or recorded in this series but was spontaneously complained of by less than five patients.

The burden of preoperative explanation and tuition to patients and parents and postoperative supervision to ensure appropriate and safe use of the patient-controlled analgesia machines was considerable in this series of patients. In the absence of dedicated staff and time to do this there would be many patients in whom a straightforward infusion is preferable to patient-controlled analgesia. This would be particularly so in smaller children aged from 5-8 years where poorly supervised patient-controlled analgesia is associated with inappropriate use of the pump resulting in poorer analgesia and more complications and problems than an infusion.

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APPENDIX 1: Published Papers

Doyle E, Robinson D, Morton NS. Comparison of Patient-Controlled Analgesia in Children with and without a Background Infusion. British Journal of Anaesthesia 1993; 71: 670-673.

Doyle E, Harper I, Morton NS. Comparison of Patient-Controlled Analgesia with different low dose Background Infusions in Children. British Journal of Anaesthesia 1993; 71: 818-822.

Doyle E, Mottart K, Marshall C, Morton NS. Patient-Controlled Analgesia in Children: Comparison of Different Bolus Doses. British Journal of Anaesthesia 1994; 72: 160-163.

Semple D, Aldridge LA, Doyle E. Comparison of the Intravenous and Subcutaneous routes of administration for Opioid Infusions in children. British Journal of Anaesthesia 1996; 76: 310-312.

Doyle E, Morton NS, McNicol LR. Comparison of Patient-Controlled Analgesia by the Intravenous and Subcutaneous routes of administration in Children. British Journal of Anaesthesia 1994; 72: 533-536.

Doyle E, Byers G, McNicol LR, Morton NS. Effect of Transdermal Hyoscine on Nausea and Vomiting during Patient-Controlled Analgesia in Children. British Journal of Anaesthesia 1994; 72: 72-76.

COMPARISON OF PATIENT-CONTROLLED ANALGESIA WITH AND WITHOUT A BACKGROUND INFUSION AFTER LOWER ABDOMINAL SURGERY IN CHILDREN

E. DOYLE, D. ROBINSON AND N. S. MORTON

SUMMARY

Forty children aged 6-12 yr undergoing appendectomy were allocated randomly to receive postoperative i.v. morphine by a patient-controlled analgesia (PCA) system (bolus dose $20 \mu\text{g kg}^{-1}$ with a lockout interval of 5 min) or the same PCA with a background infusion of morphine $20 \mu\text{g kg}^{-1} \text{h}^{-1}$. Patients breathed air and oxygen saturation was monitored by continuous pulse oximetry. Scores for pain, sedation and nausea were recorded hourly. Patients with PCA + background infusion received significantly more morphine than those with PCA only. Both groups self-administered similar amounts of morphine using the PCA machine. There were no significant differences in the pain scores of the two groups. Patients with PCA + background infusion suffered more nausea ($P < 0.01$), more sedation ($P < 0.05$) and hypoxaemia ($P < 0.001$) than those with PCA only. They also had a better sleep pattern than those with PCA only. (Br. J. Anaesth. 1993; 71: 670-673).

KEY WORDS

Analgesia: postoperative, patient-controlled. Analgesics: morphine. Anaesthesia: paediatric.

Patient-controlled analgesia (PCA) has been used in children since 1987 [1], initially in adolescents and later in selected children as young as 5 yr [2-6]. The drug used most commonly has been morphine with a bolus dose of $10-25 \mu\text{g kg}^{-1}$ and a lockout interval of 5-15 min. A continuous background infusion has been used in some studies. These studies were empirical and there are few which have compared different PCA regimens in paediatric practice.

The addition of a background infusion to PCA may improve the quality of analgesia provided [7] by reducing the decrease in plasma concentrations of opioid during sleep. However, a fixed infusion may reduce the inherent safety of PCA by continuing to deliver opioid to a patient who has adequate analgesia [8]. The use of a background infusion may also result in larger amounts of opioid being administered and an increase in the incidence of opioid-induced side effects [9].

This study was carried out to assess the effect on postoperative analgesia, sedation, ventilatory frequency, nausea and vomiting, sleeping pattern and arterial oxygen saturation (SpO_2) of adding a back-

ground infusion of morphine to a PCA regimen in children.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained. We studied 40 children aged 6-12 yr undergoing appendectomy. The patients were visited before operation when the principles of using PCA were explained to the child and parents, and the patients were taught how to use the trigger of the PCA machine.

Patients were studied only if they had not received preoperative analgesia. All patients received a standard general anaesthetic which consisted of a rapid sequence induction with thiopentone $5-7 \text{ mg kg}^{-1}$ and suxamethonium 1 mg kg^{-1} . The trachea was intubated and the patient's lungs ventilated with 67% nitrous oxide and 0.5-2% isoflurane in oxygen as indicated clinically. Neuromuscular paralysis was maintained with vecuronium 0.1 mg kg^{-1} . Morphine 0.1 mg kg^{-1} was given during operation. At the end of surgery, residual neuromuscular block was antagonized with neostigmine and glycopyrronium in appropriate doses. In the recovery area, patients were made comfortable by administration of increments of morphine $50 \mu\text{g kg}^{-1}$ if required.

Before patients left the recovery area, the PCA machine (Graseby PCAS or 3300) was connected. The solution used consisted of morphine sulphate 1 mg kg^{-1} diluted to 50 ml with 0.9% saline to give a concentration of $20 \mu\text{g kg}^{-1} \text{ml}^{-1}$. The PCA machine was attached to the side arm of a Cardiff one-way valve incorporated into the i.v. infusion cannula. The settings used were a bolus dose of 1 ml ($20 \mu\text{g kg}^{-1}$) with a lockout interval of 5 min. Patients were allocated randomly (by means of a computer-generated list) to receive either this PCA regimen or the same PCA regimen with a background infusion of morphine 1 ml h^{-1} ($20 \mu\text{g kg}^{-1} \text{h}^{-1}$).

After operation, patients breathed air and a monitoring regimen described previously [10] was used: SpO_2 , ventilatory frequency, sedation score, pain score and nausea score, the number of demands

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made and the volume of solution infused were recorded hourly. Patients were visited three times daily by one of the authors, when the correct use of the trigger was emphasized and syringes were replaced if necessary. A named anaesthetist was available to deal with any problems relating to the PCA regimens. The PCA was discontinued when there was a consistent decline in use and patients were able to take oral analgesics.

Pain was scored using a four-point self-reporting score which has been validated previously [11]: A = asleep; 0 = no pain; 1 = not really sore; 2 = quite sore; 3 = very sore. Children were not awakened for assessment unless the nurse suspected oversedation; "A" was recorded on the chart at these times.

Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open when shaken; 3 = unrousable.

Nausea was scored on a four-point scale: 0 = none; 1 = nausea only; 2 = vomited once in the past 1 h; 3 = vomited more than once in the past 1 h.

If there was a pain score of 3, a sedation score of 3 or a nausea score of 3, the named anaesthetist was asked to see the patient.

Results were analysed using the Mann-Whitney *U* test and chi-square tests as appropriate.

RESULTS

Details of the patients are shown in table I.

The total morphine consumption in the PCA + background group was significantly ($P < 0.01$)

TABLE I. Patient characteristics and details of morphine usage (number, mean (range or SD)). * $P < 0.05$ between groups

	PCA only		PCA + background
Sex (M:F)	11:9		12:8
Age (yr)	9.6 (6-12)		10.2 (6-12)
Weight (kg)	33.5 (12.6)		32.8 (9.3)
Time of operation			
06:00-22:00	11		13
22:00-06:00	9		7
Duration of PCA (h)	36.9 (11.1)		37.1 (7.4)
Morphine usage			
($\mu\text{g kg}^{-1}$)	980 (434)	*	1635 (748)
($\mu\text{g kg}^{-1} \text{ h}^{-1}$)	27.6 (12.7)	*	43.3 (14.8)
Background infusion			
($\mu\text{g kg}^{-1}$)			694 (189)
PCA ($\mu\text{g kg}^{-1}$)	980 (434)		941 (718)

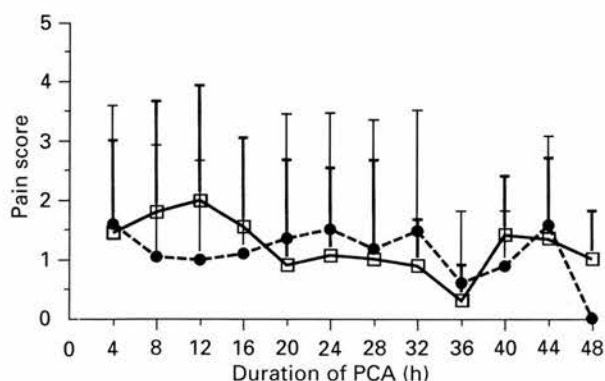


FIG. 1. Mean (SD) 4-hourly total pain scores in patients receiving PCA only (\square) or PCA + background infusion (\bullet).

greater than that in the PCA only group. There was no significant difference in the amounts of morphine self-administered in the two groups.

For each patient, the hourly pain scores during each 4-h period were summed at 4-h intervals after the start of treatment and the means for patients in the two groups calculated (fig. 1).

There were no significant differences between the scores of the two groups in any of these periods.

There were significantly more instances of SpO_2 less than 94% in the PCA + background group (143) than in the PCA only group (94) ($P < 0.001$). The smallest values of SpO_2 recorded at any time (including those noted between hourly recordings) in the two groups were in the ranges 83-95% (mean 91%) in the PCA + background group and 88-94% (mean 92%) in the PCA only group.

Four occasions when ventilatory frequency was < 10 b.p.m. were noted in the same patient who was receiving a background infusion. SpO_2 values at these times were 96%, 93%, 97% and 90%, respectively. The slowest ventilatory frequencies recorded in the two groups were 7-18 b.p.m. (mean 16 b.p.m.) in the PCA + background group and 12-20 b.p.m. (mean 17 b.p.m.) in the PCA only group.

The occurrence of sedation scores of 2 or greater were compared. There were no recordings of 3 in either group, but a significantly greater number of scores of 2 in the PCA + background infusion group (13) than in the PCA only group (4) ($P < 0.05$).

There was a significantly greater incidence of nausea and vomiting in the PCA + background group (37) than in the PCA only group (15) ($P < 0.01$). Antiemetics were given to one child in the PCA + background group.

The number of adverse events ($\text{SpO}_2 < 94\%$, sedation scores ≥ 2 , nausea and vomiting) during the first 24 h of PCA use and subsequently did not differ between the groups.

The amount of time that patients in the two groups spent asleep was compared separately for the periods from 22:00 to 06:00 (night) and from 06:00 to 22:00 (day). Patients in the PCA + background group spent significantly ($P < 0.001$) more time asleep at night (198 h) than those in the PCA only group (154 h). There was no difference between the two groups in the time spent asleep during the day. Similar numbers of patients in both groups were operated on during the day and at night. The effect of the timing of operation on sleep pattern should, therefore, have been the same in both groups.

The analgesia provided in both groups was generally very good, with only 119 scores of 2 = quite sore or 3 = very sore from a total of 1521 scores (59 of 759 scores in the PCA only group and 60 of 762 in the PCA + background infusion group).

One child in the PCA + background group had the background infusion discontinued because of persistently decreased SpO_2 when asleep, although the ventilation frequency was always 14 b.p.m. or greater.

DISCUSSION

Since its first use in children in 1987, PCA has become a widely used and effective treatment for

acute pain in selected children as young as 5 yr. Most reports of its use in children are, however, simply descriptive and there are few controlled studies which compare different regimens in terms of efficacy, dosage and adverse effects.

The use of a concurrent background infusion with PCA in adults is currently an area of debate in the literature. It has been shown to improve pain relief in two studies [12, 13]. In one of these [12], the use of a background infusion after abdominal hysterectomy not only improved analgesia but was associated with improved sleep patterns and increased patient satisfaction without an increase in opioid-induced side effects. The other study [13] found that the use of a background infusion improved analgesia but was associated with an increase in opioid-related side effects such as nausea and vomiting. Significant respiratory depression was not observed.

Other studies have shown no benefit when a background infusion was added to the PCA regimen [14–16]. In these patients, morphine consumption was increased with no improvement in analgesia. The incidence of side effects was not increased and respiratory depression was not noted in the group receiving a background infusion.

In paediatric practice, one study [17] has compared PCA with and without a background infusion (in a comparison with i.m. injections). In that study, the infusion used was morphine $15 \mu\text{g kg}^{-1} \text{h}^{-1}$. The PCA only group received bolus doses of $25 \mu\text{g kg}^{-1}$ and the PCA + background infusion group received bolus doses of morphine $18 \mu\text{g kg}^{-1}$. In both groups, lockout time was 10 min. There were no differences in morphine consumption, sedation, nausea or vomiting between the groups. Respiratory depression was not noted in any patient. The PCA + background group was found to have smaller pain scores than the PCA only group. This study used patient and nursing visual analogue scores for pain assessment, whereas our study used a patient self-report scale; this may account for the different findings of the two studies. Another study [18] in children found that PCA + background infusion did not improve analgesia, but was associated with a better sleep pattern than PCA alone, with no increase in the incidence of side effects.

Our study has found that the use of a background infusion of morphine $20 \mu\text{g kg}^{-1} \text{h}^{-1}$ in a PCA regimen for children undergoing lower abdominal surgery produced a significant increase in morphine consumption without improving pain relief, and a significant increase in the incidence of side effects (respiratory depression, over-sedation and nausea or vomiting). Patients in the PCA + background group spent more time asleep at night than those in the PCA only group. There was no suggestion that the incidence of side effects increased with the duration of PCA use as the severity of postoperative pain declined.

The great variability in the morphine requirements of our patients, who had all undergone the same operation, is shown by the large standard deviation in the amount of morphine self-administered. The use of a fixed dose of morphine to cope with this wide variability would be expected to be

unsuccessful. This may be why the use of a relatively small fixed infusion in addition to the PCA produced no discernible improvement in analgesia.

This is the first study to have shown an increased incidence of respiratory depression in patients receiving a background infusion compared with those receiving PCA only. Respiratory depression has been considered to be one risk associated with the addition of an infusion to PCA, but has not previously been shown to occur. The reason for this is probably that the previous studies comparing PCA with and without a background infusion [12–17] and the descriptive publications of patients receiving PCA + background have relied on intermittent timing of ventilatory frequency as an indicator of respiratory depression. This has been shown to be a late and insensitive monitor of respiratory depression [19, 20]. Arterial oxygen saturation (SaO_2) while breathing air is a more sensitive monitor of adequate ventilation and it has been suggested that pulse oximetry should be routine for the monitoring of children receiving PCA [21]. An SaO_2 of 94% corresponds to a PaO_2 of 10 kPa in healthy patients and indicates mild hypoxia and reduced reserve should further respiratory depression occur.

The use of PCA in adults also is associated with an incidence of respiratory depression. This may occur in up to 40% of patients breathing air after upper abdominal surgery [22]. Patients using PCA after lower abdominal surgery have been shown to be more likely to suffer episodes of mild hypoxaemia than patients receiving i.m. or extradural morphine [23]. Other studies have shown no difference between the incidences of hypoxaemia in adults receiving PCA and those receiving i.m. morphine [22].

In our study, 15% of SpO_2 values were less than 94% in the PCA only group. The significance of this is unclear as there is no information on the incidence of hypoxaemia detected by pulse oximetry in children breathing air and given i.m. opioids.

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PATIENT-CONTROLLED ANALGESIA WITH LOW DOSE BACKGROUND INFUSIONS AFTER LOWER ABDOMINAL SURGERY IN CHILDREN

E. DOYLE, I. HARPER AND N. S. MORTON

SUMMARY

Forty-five children (aged 6–12 yr) undergoing appendicectomy received one of three analgesic regimens using patient-controlled analgesia (PCA) with morphine: no background infusion (B0); background infusion $4 \mu\text{g kg}^{-1} \text{h}^{-1}$ (B4); background infusion $10 \mu\text{g kg}^{-1} \text{h}^{-1}$ (B10). Total consumption of morphine was greater in group B10 compared with groups B0 ($P < 0.01$) and B4 ($P < 0.05$). There was no significant difference in morphine consumption in groups B0 and B4. All three groups self-administered similar amounts of morphine and there were no significant differences in pain scores or incidence of excessive sedation. Group B4 suffered less hypoxaemia compared with groups B0 ($P < 0.01$) and B10 ($P < 0.001$). Group B10 suffered more nausea and vomiting than groups B0 ($P < 0.001$) and B4 ($P < 0.001$), but there was no significant difference in the incidence of nausea and vomiting between groups B0 and B4. Groups B4 and B10 spent more time at night asleep than group B0 ($P < 0.05$). There were no significant differences between the groups in the amount of time spent asleep during the day. Inclusion of a background infusion of morphine $4 \mu\text{g kg}^{-1} \text{h}^{-1}$ in a PCA regimen for children did not increase the incidence of side effects and was associated with less hypoxaemia and a better sleep pattern than no background infusion. (Br. J. Anaesth. 1993; 71: 818–822)

KEY WORDS

Analgesia: patient-controlled. Vomiting, nausea.

Patient-controlled analgesia (PCA) is now used in children as young as 5 yr for the treatment of postoperative pain [1]. The drug used most commonly is morphine, in a bolus dose of $10\text{--}25 \mu\text{g kg}^{-1}$ and a lockout interval of 5–15 min. These settings are empirical and there are few well conducted studies which have compared different PCA regimens in paediatric practice. In particular, the benefits and risks of background infusions have not been defined. Adult studies give conflicting results [2–6] and one study in children [7] found an improvement in analgesia without an increase in side effects with a background infusion of morphine

$15 \mu\text{g kg}^{-1} \text{h}^{-1}$. A more recent paediatric study [8] found that a background infusion of morphine $20 \mu\text{g kg}^{-1} \text{h}^{-1}$ did not improve pain scores, but was associated with a better sleep pattern. However, the background infusion was associated with a greater incidence of hypoxaemia, excessive sedation, nausea and vomiting compared with the PCA-only regimen.

This study was carried out to assess the effect of two different low-dose background infusions on postoperative analgesia, sleep pattern, morphine consumption, sedation, nausea, vomiting, respiratory depression and arterial oxygen saturation in air (SpO_2).

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained. On the basis of previous work using this methodology [8], it was calculated that this study had a 90% probability of detecting differences between groups which would be significant at the 5% level. Forty-five children aged 6–12 yr undergoing appendicectomy were recruited. Patients were visited before operation, when the principles of using PCA were explained to the child and parents. Patients were taught to use the trigger of the PCA machine during this visit. Patients were not studied if they had received preoperative analgesia.

All patients received a standard general anaesthetic which comprised rapid sequence induction with thiopentone $5\text{--}7 \text{mg kg}^{-1}$ and suxamethonium 1mg kg^{-1} . The trachea was intubated and the patient's lungs ventilated with 67% nitrous oxide and 0.5–2.0% isoflurane in oxygen as indicated clinically. Neuromuscular block was maintained with vecuronium 0.1mg kg^{-1} . Morphine 0.1mg kg^{-1} was given during operation. At the end of surgery, neuromuscular block was antagonized with neostigmine and glycopyrronium in appropriate doses. In the recovery area, patients were made comfortable with boluses of morphine $50 \mu\text{g kg}^{-1}$ if required.

Before the patient left the recovery area, the PCA pump was set up (Graseby PCAS and Graseby 3300). The solution consisted of morphine 1mg kg^{-1}

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TABLE I. Patient characteristics and details of morphine consumption (mean (range or SD)). Significant differences compared with group B10: * $P < 0.05$; ** $P < 0.01$

	Group B0	Group B4	Group B10
Sex (M:F)	7:8	8:7	10:5
Age (yr)	10.5 (8.7–12.1)	10.4 (6.5–12.9)	10.3 (7.2–12.4)
Weight (kg)	35.5 (9.0)	35.9 (6.8)	40.0 (10.7)
Time of operation			
06:00–22:00	10	9	10
22:00–06:00	5	6	5
Duration of PCA use (h)	38.5 (5.2)	42.7 (9.5)	45.4 (12.6)
Total morphine consumption			
($\mu\text{g kg}^{-1}$)	880 (389)**	1080 (467)*	1524 (619)
($\mu\text{g kg}^{-1} \text{ h}^{-1}$)	23.5 (10.8)**	25.4 (9.2)*	35.9 (18.9)
Self-administered morphine			
($\mu\text{g kg}^{-1}$)	880 (389)	910 (452)	1062 (638)
($\mu\text{g kg}^{-1} \text{ h}^{-1}$)	23.5 (10.8)	21.4 (9.2)	25.9 (18.9)

diluted to 50 ml with 0.9 % saline ($20 \mu\text{g kg}^{-1} \text{ ml}^{-1}$). The PCA machine was attached to the side arm of a Cardiff one-way valve incorporated into the i.v. infusion cannula. Patients were allocated randomly (computer-generated list) to receive one of three different PCA regimens: group B0 received bolus doses of morphine $20 \mu\text{g kg}^{-1}$ with a lockout interval of 5 min and no background infusion; group B4 received bolus doses of $20 \mu\text{g kg}^{-1}$ with a lockout interval of 5 min and a background infusion of morphine $4 \mu\text{g kg}^{-1} \text{ h}^{-1}$; group B10 received bolus doses of $20 \mu\text{g kg}^{-1}$ with a lockout interval of 5 min and a background infusion of $10 \mu\text{g kg}^{-1} \text{ h}^{-1}$.

After operation, patients breathed air and a monitoring regimen described previously [9] was used. This involved a high dependency level of nursing care with hourly recordings of Sp_{O_2} , ventilatory frequency and sedation, pain and nausea scores. The number of demands made and the volume of solution infused were also recorded hourly. Patients were reviewed regularly by one of the authors. There was always a named anaesthetist available to deal with any problems relating to the PCA regimen. PCA was discontinued when there was a consistent decline in use and the patient was able to take oral analgesics.

Pain was measured using a four-point, self-reporting score which has been validated previously [10]: 0 = no pain; 1 = not really sore; 2 = quite sore; 3 = very sore.

Children were not awakened from sleep for assessment unless the nurse suspected excessive sedation and "A" was recorded on the chart at these times. Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open when shaken; 3 = unrousable.

We considered patients to be sedated excessively if they were not rousable by speech and required to be shaken. Experienced paediatric nurses were able to differentiate between a child who was asleep naturally and one who was sedated excessively as a result of opioid.

Nausea was scored on a four-point scale: 0 = none; 1 = nausea only; 2 = vomited once in the past 1 h; 3 = vomited more than once in the past 1 h.

If there was a pain score of 3, a sedation score of 3 or a nausea score of 3, the named anaesthetist was asked to see the patient.

Results were analysed using analysis of variance and the Mann-Whitney U test for pain scores and morphine consumption, and chi-square tests for comparisons of events between groups.

RESULTS

Patient characteristics are shown in table I.

Two patients in group B0, one in group B4 and one in group B10 received a bolus of morphine $50 \mu\text{g kg}^{-1}$ in the recovery area. These boluses were not included in the figures for postoperative consumption of morphine.

Patients in all three groups self-administered similar amounts of morphine using the PCA machine. Total morphine consumption was significantly greater in group B10 compared with groups B0 ($P < 0.01$) and B4 ($P < 0.05$). Group B4 self-administered $2 \mu\text{g kg}^{-1} \text{ h}^{-1}$ less than group B0; thus when the background infusion is taken into account, group B4 received $2 \mu\text{g kg}^{-1} \text{ h}^{-1}$ more morphine than group B0.

For each patient, the hourly pain scores during each 4-h period after the start of the PCA regimen were totalled. The mean 4-hourly totals for patients in the three groups are shown in figure 1. There were no significant differences between the scores of the three groups during any of these periods.

Table II shows the numbers of patients in each group who were receiving PCA at the end of each 12-h period after operation.

Sp_{O_2} readings were accepted as valid and recorded only if they were consistent over 2–3 min and there was a good pulse signal on the oximeter screen. The occurrence of hypoxaemic episodes (defined as $\text{Sp}_{\text{O}_2} < 94\%$) in the three groups is shown in table III. Group B10 had significantly more recordings less than 94 % compared with groups B0 ($P < 0.001$) and B4 ($P < 0.001$). Group B0 had significantly more recordings less than 94 % compared with group B4 ($P < 0.01$). The smallest Sp_{O_2} values in the three groups were 86–95 % (mean 91.6 %) in group B0, 86–95 % (mean 92.4 %) in group B4 and 86–95 % (mean 90.3 %) in group B10.

The slowest ventilatory frequencies recorded in the three groups were 12–18 b.p.m. in group B0, 12–20 b.p.m. in group B4 and 14–18 b.p.m. in group B10.

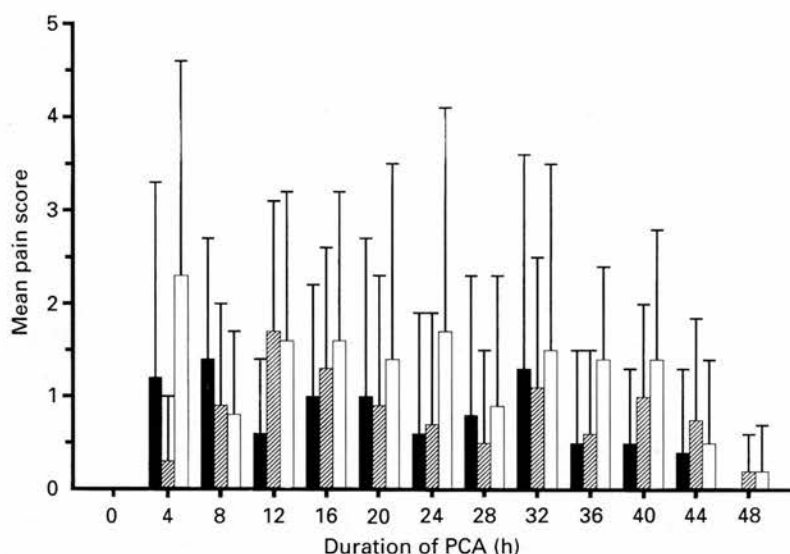


FIG. 1. Mean (SD) 4-hourly total pain scores in groups B0 (■), B4 (▨) and B10 (□).

TABLE II. Numbers of patients in each group using PCA after each 12-h interval after operation

	Group B0	Group B4	Group B10
12 h	15	15	15
24 h	15	15	15
36 h	13	13	14
48 h	2	4	3

TABLE III. Comparison of incidence of Sp_{O_2} readings less than 94% in the three groups. **Significantly greater than group B4 ($P < 0.01$, $\chi^2 = 6.9$); ***significantly greater than B0 and B4 ($P < 0.001$, $\chi^2 = 51$)

	Group B0	Group B4	Group B10
$Sp_{O_2} < 94\%$	78**	56	159***
$Sp_{O_2} \geq 94\%$	499	583	523

TABLE IV. Comparison of the incidence of emetic sequelae in the three groups. ***Significant difference ($P < 0.001$) compared with groups B0 ($\chi^2 = 16.2$) and B4 ($\chi^2 = 14.9$)

	Group B0	Group B4	Group B10
Episodes of emetic sequelae	20	22	60***
No. of patients who complained of emetic sequelae	8	8	10

TABLE V. Comparison of duration of sleep between 22:00 and 06:00 (night) and between 06:00 and 22:00 (day) in the three groups. *Significant difference ($P < 0.05$) compared with groups B4 ($\chi^2 = 5.3$) and B10 ($\chi^2 = 5.3$)

	Group B0	Group B4	Group B10
Night			
Asleep	142*	178	217
Awake	78	61	68
Day			
Asleep	85	92	86
Awake	272	308	311

A sedation score of 3 was not recorded in any patient. A sedation score of 2 occurred on 22 occasions in group B0, 19 in group B4 and on 21 occasions in group B10 (not significant).

Group B10 suffered significantly more emetic sequelae than groups B0 ($P < 0.001$) and B4 ($P < 0.001$) (table IV). There was no significant difference in the incidence of emetic sequelae between groups B0 and B4. Antiemetics were given to one patient in group B10.

The amount of time spent asleep was compared in the three groups by analysing the periods from 22:00 (after the evening ward drug round) to 06:00 (night) and from 06:00 to 22:00 (day) separately. Groups B4 and B10 spent significantly more time asleep at night compared with patients in group B0 ($P < 0.05$). There was no significant difference between groups B4 and B10 in the amount of time spent asleep at night, and no significant differences between the groups in the amount of time spent asleep during the day (table V). Similar numbers of patients in all groups were operated upon during the day and at night.

Three patients in group B10 had the background infusion discontinued because of persistent excessive sedation.

DISCUSSION

There are few controlled studies which have compared different PCA regimens for children in terms of efficacy, dosage and adverse effects. The role for a background infusion with PCA has not been defined clearly. The perceived advantage of using a background infusion is that it improves continuity of analgesia and provides analgesia during sleep. This may improve sleep patterns in postoperative patients by reducing the number of occasions when patients are awakened by pain which requires subsequent use of the PCA device for relief.

The operation of appendectomy provides a good model for the study of postoperative analgesic regimens. It involves a standard surgical procedure and a degree of peritoneal irritation which ensures

that postoperative morphine requirements when self-administered with a PCA machine are of the order of $20\text{--}30\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$, which is the same as that in children after more major abdominal and orthopaedic surgery [11–14].

This study has shown that the use of a background infusion of morphine $4\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$ in a PCA regimen for children after lower abdominal surgery caused no increase in side effects compared with no background infusion and was associated with less hypoxaemia and a better sleep pattern than PCA only. A background infusion of morphine $10\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$ was associated with a better sleep pattern also, but was accompanied by a significant increase in the incidence of hypoxaemia and nausea and vomiting. Unlike a background infusion of $20\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$ [8], these smaller infusion rates were not associated with an increase in the incidence of excess sedation.

The reason why a background infusion of morphine $4\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$ produces less hypoxaemia than a PCA regimen with no background infusion may be that the infusion produced better analgesia and improved ventilation. This suggests that the method for assessing pain used in this study (patient self-report) is relatively insensitive. A specific assessment of pain on moving or coughing may have revealed differences in analgesia between groups B0, B4 and B10. We have also previously noted that periods of hypoxaemia often correspond with high pain scores [9].

In adult studies, the use of a background infusion has been shown to improve pain relief in two studies [2, 3], but not in others [4–6]. The studies which found no benefit from a background infusion did not assess pain during movement. In contrast, one of the studies which did find improved analgesia with a background infusion [3] did assess pain on movement. The other study [2] did not make clear if pain was assessed only at rest or during movement. Two studies [3, 5] found an increase in opioid-induced side effects (other than respiratory depression) with a background infusion. The size of background infusion of morphine varied from 0.6 mg h^{-1} to 1.5 mg h^{-1} (pethidine 10 mg h^{-1} in one), which is equivalent to $10\text{--}20\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$.

In paediatric practice, two studies [7, 8] have compared PCA with and without a background infusion. In one [7] the infusion used was morphine $15\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$ and there were no differences in morphine consumption, sedation, nausea or vomiting. Respiratory depression (as measured by ventilatory frequency) was not noted in any patient. The PCA plus background infusion group were found to have smaller pain scores than the PCA only group as assessed by patient and nurse visual analogue scales.

In the other study [8], a background infusion of morphine $20\text{ }\mu\text{g kg}^{-1}\text{ h}^{-1}$ produced a significant increase in morphine consumption without improving pain scores (assessed by patient self-report). There was also a significant increase in the incidence of opioid-induced side effects (respiratory depression, excessive sedation, nausea and vomiting) in the background infusion group. However, the use of a background infusion was associated with a better sleep pattern.

Opioid-induced respiratory depression has been considered to be a risk of background infusion, but has been shown to occur only in one paediatric study [8] when SpO_2 was measured continuously with patients breathing air. Intermittent recording of ventilatory frequency has been shown to be an insensitive monitor of opioid-induced respiratory depression in adults [15–17]. Studies which have relied on intermittent recording of ventilator frequency as an indicator of respiratory depression and have concluded that a background infusion does not produce respiratory depression [2–7] may be falsely optimistic. Arterial oxygen saturation while breathing air is a more sensitive monitor of adequate ventilation. SpO_2 94% corresponds to an arterial oxygen tension of 10 kPa and indicates mild hypoxaemia. In the absence of other causes of hypoxaemia, this indicates a degree of ventilatory depression which may be caused by opioid administration or pain. In our experience, pain is a more common reason for hypoxaemia than opioid overdosage. This emphasizes the need for careful and repeated assessments by experienced staff.

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Comparison of different bolus doses of morphine for patient-controlled analgesia in children

E. DOYLE, K. J. MOTTART, C. MARSHALL AND N. S. MORTON

SUMMARY

Forty children undergoing appendicectomy were allocated randomly to receive one of two PCA regimens with morphine. Group B10 received bolus doses of $10 \mu\text{g kg}^{-1}$ and group B20 received bolus doses of $20 \mu\text{g kg}^{-1}$. In both groups there was a lockout interval of 5 min and a background infusion of $4 \mu\text{g kg}^{-1} \text{ h}^{-1}$. Group B20 self-administered considerably more morphine ($P < 0.01$) than group B10. There was no difference between the pain scores of the groups at rest. Group B20 had significantly ($P < 0.05$) smaller pain scores during movement than group B10 and the latter group suffered significantly ($P < 0.01$) more hypoxaemic episodes than group B20. There were no differences between the groups in the incidence of vomiting, excess sedation or the amount of time spent asleep at night. (Br. J. Anaesth. 1994; 72: 160–163)

KEY WORDS

Analgesia: patient-controlled. Analgesics, opioid: morphine. Anaesthesia: paediatric.

Patient-controlled analgesia (PCA) is now used commonly for the treatment of acute pain in selected children [1]. Regimens described have used bolus doses of morphine ranging from 10 to $50 \mu\text{g kg}^{-1}$ [2–6], but there have been no comparative studies of different bolus doses in children in terms of efficacy and side effects.

This study was carried out to compare bolus doses of $10 \mu\text{g kg}^{-1}$ and $20 \mu\text{g kg}^{-1}$ in a PCA regimen for children, in terms of efficacy, morphine consumption and side effects. The PCA regimen used included a background infusion of $4 \mu\text{g kg}^{-1} \text{ h}^{-1}$, which has been shown to be superior to a PCA regimen without a background infusion in children [7].

A pain scoring system which assesses pain only at rest does not discriminate well between different analgesic regimens [7]. This study was designed to include an assessment of pain both during movement and at rest, to improve sensitivity.

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained for all patients. We studied 40 children aged 6–14 yr undergoing appendicectomy. Operations were performed as urgent procedures in the

first available operating theatre when the patient had been adequately hydrated. Patients were visited before operation when the principles of using PCA were explained to the child and parents. Patients were taught to use the trigger of the PCA machine during this visit. Preoperative analgesia was prescribed by surgical staff on clinical grounds without reference to this study. Patients were not recruited if analgesia had been prescribed at the time of the preoperative visit.

All patients received a standard general anaesthetic (with no premedication) which consisted of a rapid sequence induction with thiopentone $5\text{--}7 \text{ mg kg}^{-1}$ and suxamethonium 1 mg kg^{-1} . The trachea was intubated and the patient's lungs ventilated with 67% nitrous oxide and 0.5–2.0% isoflurane in oxygen. Neuromuscular block was maintained with vecuronium 0.1 mg kg^{-1} . Morphine 0.1 mg kg^{-1} was given during operation. At the end of surgery neuromuscular block was antagonized with neostigmine $50 \mu\text{g kg}^{-1}$ and glycopyrronium $10 \mu\text{g kg}^{-1}$. In the recovery area, the patient was titrated to comfort with boluses of morphine $50 \mu\text{g kg}^{-1}$ if required.

Before the patient left the recovery area, the PCA pump (Graseby PCAS) was set up. The solution used consisted of morphine 1 mg kg^{-1} diluted to 50 ml with 0.9% saline to give a concentration of $20 \mu\text{g kg}^{-1} \text{ ml}^{-1}$. The PCA machine was attached to the side arm of a Cardiff one-way valve incorporated into the i.v. infusion system. Patients were allocated randomly (by means of a computer-generated list) to receive one of two different PCA regimens: group B10 received bolus doses of morphine $10 \mu\text{g kg}^{-1}$ with a lockout interval of 5 min and a background infusion of $4 \mu\text{g kg}^{-1} \text{ h}^{-1}$; group B20 received bolus doses of morphine $20 \mu\text{g kg}^{-1}$ with a lockout interval of 5 min and a background infusion of $4 \mu\text{g kg}^{-1} \text{ h}^{-1}$.

After operation the patient breathed air. A monitoring procedure described previously [8] was used, involving a high-dependency level of nursing care with hourly recordings of SpO_2 , ventilatory frequency, sedation score, pain score and nausea score. The number of demands made and the volume of solution infused were also recorded hourly. Patients were reviewed three times a day by one of the

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authors. There was always a named anaesthetist available to deal with any problems relating to the PCA regimens. PCA was discontinued when there was a consistent decline in use and the patient was able to take oral analgesics.

Pain was scored both at rest and during a specified movement, by observers who were unaware of the patient's treatment group. Pain at rest was scored using a four-point, self-reporting score which has been validated previously [9] as follows: 0 = no pain; 1 = not really sore; 2 = quite sore; 3 = very sore.

Pain on movement was scored using the same scoring system during a vital capacity breath followed by a cough. Children were not awakened from sleep for assessment unless the nurse suspected oversedation; "A" was recorded on the chart at these times. Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open when shaken; 3 = unrousable.

Nausea was scored on a four-point scale: 0 = none; 1 = nausea only; 2 = vomited once in the past 1 h; 3 = vomited more than once in the past 1 h.

If there was a pain score of 3, a sedation score of 3 or a nausea score of 3, the named anaesthetist was asked to attend the patient.

Results were analysed using the Mann-Whitney U test for pain scores and morphine consumption and chi-square tests for comparisons of events between groups.

RESULTS

The two groups were similar in age, weight, sex distribution, duration of PCA use and timing of surgery (table I). Patients in group B20 self-administered significantly more morphine than those in group B10 ($P < 0.01$). There was no significant difference between the groups in the percentage of unsuccessful demands for analgesia (those which were made during the lockout period). Table II shows the number of patients in each group who were still using PCA at the end of each 12-h period after operation.

Pain scores were compared by calculating the mean hourly pain score during each 4-h period after operation and comparing the groups during each of these periods. There were no significant differences between the groups at rest at any time except for the period 16–20 h after operation, when the difference just reached significance at the 5 % level (fig. 1). Pain scores during movement in group B20 were significantly ($P < 0.05$) smaller than those in group B10 during each 4-h period, except for that between 44 and 48 h after operation (fig. 2). At 44–48 h after operation no patient in group B20 complained of pain at rest, although some did have pain on movement.

There were significantly more Sp_{O_2} recordings less than 94 % in group B10 than in group B20 ($P < 0.01$) (table III). Readings were regarded as valid

TABLE I. Patient data and details of morphine consumption (mean (range or SD)). ** $P < 0.01$ between groups

	Group B10		Group B20
Sex (M:F)	12:8		10:10
Age (months)	128 (95–150)		123 (93–151)
Weight (kg)	33.9 (7.2)		35.1 (9.9)
Time of surgery			
06:00–22:00	12		10
22:00–06:00	8		10
Duration of PCA use (h)	43 (7.8)		41 (6.6)
Morphine consumption			
($\mu\text{g kg}^{-1}$)	505 (224)	**	1124 (691)
($\mu\text{g kg}^{-1} \text{ h}^{-1}$)	16 (5.8)	**	30.4 (14.0)
Self-admin. by PCA	12 (5.8)	**	26.4 (14.0)
($\mu\text{g kg}^{-1} \text{ h}^{-1}$)			
Successful demands (%)	71 (17)		76.6 (16.4)

TABLE II. Numbers of patients in groups B10 and B20 using PCA at the end of each 12-h period after operation

Time after op.	No. using PCA	
	Group B10	Group B20
12 h	20	20
24 h	20	20
36 h	17	19
48 h	5	3

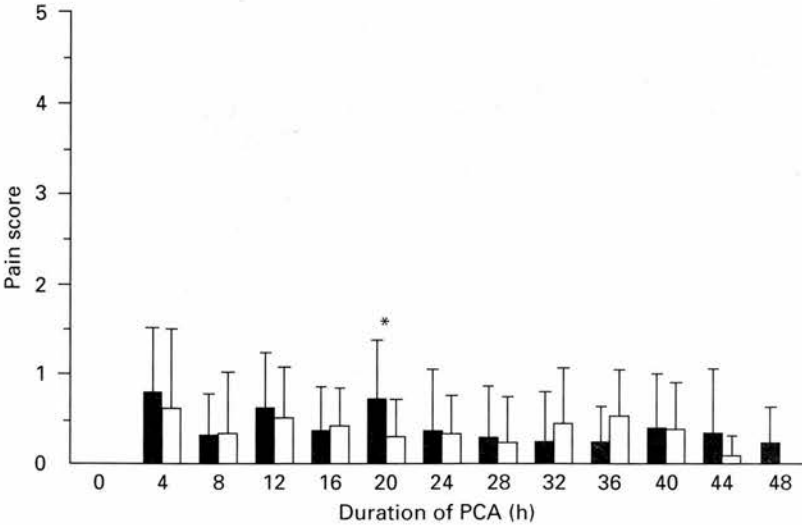


FIG. 1. Mean (SD) hourly pain scores at rest in patients in groups B10 (■) and B20 (□). * $P < 0.05$ between groups.

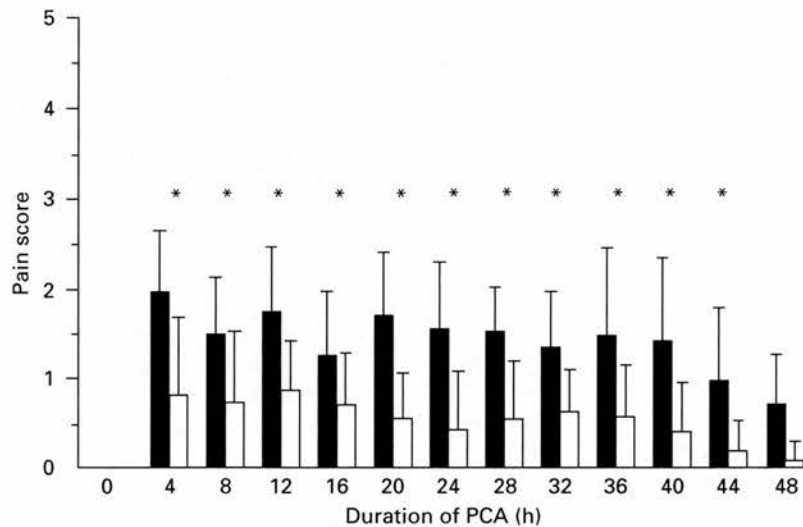


FIG. 2. Mean (SD) hourly pain scores on movement in groups B10 (■) and B20 (□). * $P < 0.05$ between groups.

TABLE III. Comparison of the incidence (absolute numbers of episodes) of Sp_{O_2} recordings of less than 94% in groups B10 and B20. $\chi^2 = 8.1$; $P < 0.01$

	Group B10	Group B20
$Sp_{O_2} < 94\%$	92	61
$Sp_{O_2} \geq 94\%$	738	798

TABLE IV. Comparison of absolute number of occasions after operation on which patients in groups B10 and B20 vomited and the amount of time spent asleep between 22:00 and 06:00 (night) and between 06:00 and 22:00 (day). No significant differences between groups

	Group B10	Group B20
Episodes of vomiting (No.)	6	3
Sleep at night (h)		
Asleep	207	200
Awake	140	134
Sleep during day (h)		
Asleep	95	89
Awake	417	407

and recorded only if they persisted for 5 min, if there was a good pulse signal on the oximeter screen and artefact caused by poor positioning or venous engorgement had been excluded.

There was no significant difference in the incidence of vomiting in the two groups after operation (table IV).

The amount of time that patients spent asleep was assessed by comparing the periods from 22:00 to 06:00 (night) and from 06:00 to 22:00 (day) separately. There was no significant difference between the groups in these periods (table IV).

There were no episodes of oversedation in any patient in each group.

DISCUSSION

The optimal bolus dose for use with PCA has been defined as the minimum dose which produces adequate analgesia consistently without causing subjective or objective side effects [10]. An in-

adequate bolus dose tends to result in inadequate analgesia, while too large a bolus may cause excessive side effects. Ideally, the patient should not be required to make too frequent demands in order to attain adequate analgesia.

This study has shown that a bolus dose of morphine $10 \mu\text{g kg}^{-1}$ was associated with greater pain scores and more hypoxic episodes than a bolus dose of $20 \mu\text{g kg}^{-1}$. There was no difference between the groups in the incidence of other opioid-induced side effects, sleep pattern or the percentage of unsuccessful demands for analgesia.

These findings are in agreement with those in adult studies in which inadequate bolus doses were associated with increased pain scores [10,11]. In those studies patients did not use the PCA device to achieve satisfactory analgesia, despite the fact that there was the facility to self-administer more analgesic. This suggests that patients do not usually use PCA to titrate analgesic drugs to a minimum effective analgesic concentration. The time since the previous analgesic demand and the expected benefit from a demand, in terms of analgesia, appear to be important factors in the frequency of patient demands [12]. If patients do not use PCA in response to pain and are prepared to suffer pain on occasion rather than use the PCA pump, studies in which the efficacy of alternative analgesic regimens is assessed by means of the morphine-sparing effect as judged by self-administered PCA morphine consumption may be unreliable.

Many of the decreased Sp_{O_2} readings noted were associated with greater pain scores and the finding of an increased incidence of decreased Sp_{O_2} in group B10 is presumably caused by inadequate ventilation as a consequence of pain leading to restriction of abdominal movement. This association of hypoxaemia with increased pain scores has been noted previously [8]. An Sp_{O_2} reading of 94% corresponds with an arterial oxygen tension of about 10 kPa and, in otherwise healthy patients breathing air, indicates a mild degree of ventilatory depression. This may be caused by pain leading to inhibition of ventilatory movement or by a relative overdosage of opioid.

There were no differences between the groups in pain scores at rest, although pain scores on movement were significantly different. This supports the suggestion that, in studies of analgesic regimens, pain scores at rest are not sufficiently sensitive to discriminate between regimens and such studies should include an assessment of pain on movement [7].

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Comparison of i.v. and s.c. diamorphine infusions for the treatment of acute pain in children

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Summary

We have compared the i.v. and s.c. routes of administration for diamorphine infusions in children undergoing abdominal surgery. Subjects received general anaesthesia with extradural block and diamorphine up to $20 \mu\text{g kg}^{-1} \text{h}^{-1}$ after operation. There were no differences between the groups in diamorphine consumption, pain scores or incidence of side effects. The s.c. route appeared to be as effective and safe as the i.v. route for administration of diamorphine infusions in children undergoing elective surgery. (*Br. J. Anaesth.* 1996; **76**: 310-312)

Key words

Analgesia, paediatric. Analgesic techniques, i.v. Analgesic techniques, s.c. Analgesics opioid, diamorphine. Pain, postoperative.

The use of i.v. opioid infusions to treat postoperative pain in children is a common and effective analgesic technique [1]. It requires a dedicated i.v. cannula for opioid administration in addition to one for i.v. fluids and drugs. Alternatively, the same cannula may be used for both fluids and opioid administration if an antireflux valve is used. The option of a second i.v. cannula is not always available, particularly in infants, while antireflux valves are expensive and make the infusion site bulky and difficult to nurse.

An alternative route of administration for opioid infusions which does not have these disadvantages is the s.c. route. This is used extensively in terminal and chronic pain and has also been described for the management of acute pain in adults [2]. The efficacy of s.c. infusions in children has been demonstrated recently [3]. For this technique to become widespread and accepted it must be shown to be as effective as the i.v. route with the same or a lower incidence of side effects. The i.v. and s.c. routes of administration have not been compared in children. This study was designed to compare these two routes in children undergoing abdominal surgery. On the basis of previous work using similar methodology [4] the power calculated for the study was that it would have a 90% chance of detecting differences between the groups which were significant at the 5% level.

Methods and results

The study was approved by the local Ethics Committee and written informed parental consent was obtained for each subject. We studied 30

children, aged 6 months to 11 yr, undergoing abdominal surgery. Exclusion criteria included contraindications to extradural block, significant hepatic or renal impairment, and significant mental handicap making assessment of pain difficult. Patients were premedicated with EMLA cream and anaesthesia was induced with propofol $3-4 \text{ mg kg}^{-1}$ and atracurium 0.5 mg kg^{-1} . After tracheal intubation, the lungs were ventilated with 0.5-2% halothane and 70% nitrous oxide in oxygen. Patients were then turned to the right lateral position and an extradural catheter placed at an appropriate dermatomal level for the proposed surgery. Extradural block was provided with 0.25% bupivacaine 1 ml kg^{-1} with adrenaline $1/200000$ (maximum 20 ml) in divided doses. At the end of surgery, neuromuscular block was antagonized and the trachea extubated.

Patients were allocated randomly to receive either an i.v. or an s.c. infusion of diamorphine after operation. In the i.v. group (group IV), a second 22-gauge cannula was sited on the same side as the cannula used for induction. In the s.c. group (group SC), a 22-gauge cannula was sited s.c. over the deltoid muscle on the same side as the i.v. cannula.

In group IV the solution used consisted of diamorphine 1 mg kg^{-1} diluted in 50 ml of 0.9% saline to give a concentration of $20 \mu\text{g kg}^{-1} \text{ml}^{-1}$. This was commenced at a rate of 1 ml h^{-1} ($20 \mu\text{g kg}^{-1} \text{h}^{-1}$). In group SC the solution used consisted of diamorphine 1 mg kg^{-1} diluted in 20 ml of 0.9% saline to give a concentration of $50 \mu\text{g kg}^{-1} \text{ml}^{-1}$. This was commenced at 0.4 ml h^{-1} ($20 \mu\text{g kg}^{-1} \text{h}^{-1}$). Diamorphine infusions were started in the recovery area. Infusions were delivered using a Graseby MS2000 pump.

After operation we used a monitoring regimen described previously [5]. Patients breathed air and had continuous monitoring of arterial oxygen saturation. We measured hourly values of ventilatory frequency, pain score, sedation score, nausea score and volume of diamorphine infused. Diamorphine was infused at a maximum rate of $20 \mu\text{g kg}^{-1} \text{h}^{-1}$ and boluses of diamorphine $50 \mu\text{g kg}^{-1}$ were available if required.

Pain was assessed by a small group of experienced paediatric surgical nurses and measured using a

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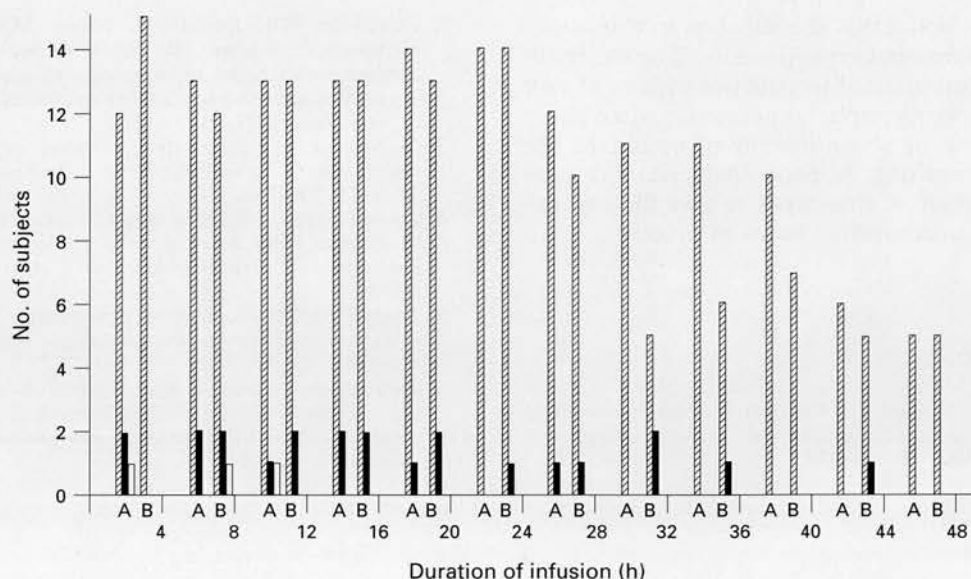


Figure 1 Comparison of pain scores (\square = 1, \blacksquare = 2, \square = 3) in groups IV (A) and SC (B).

four-point scale described previously [6]: 1 = no pain; 2 = mild pain; 3 = moderate pain; 4 = severe pain. Children were not wakened from sleep for assessments unless the nurse suspected excessive sedation. Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open in response to speech; 2 = eyes open when shaken; 3 = unrousable. Vomiting was scored on a three-point scale: 0 = none; 1 = vomited once in the last hour; 2 = vomited more than once in the last hour.

Infusions were discontinued when there was a consistent decline in diamorphine requirements and patients were able to take oral analgesics. Results were analysed using the Student's *t* test for parametric data and the Mann-Whitney *U* test for non-parametric data.

The two groups were similar in characteristics (mean age 36 months in group IV and 33 months in group SC), surgical procedures (eight gastrointestinal, two pyeloplasties, three nephrectomies and two ureteric reimplantations in group IV and six gastrointestinal, two pyeloplasties, five nephrectomies and two ureteric reimplantations in group SC) and duration of surgery (median 80 min in group IV and 65 min in group SC).

The duration of infusion analgesia (median 41 h in group IV and 39 h in group SC) and total diamorphine consumption (median 680 (range 220–1120) $\mu\text{g kg}^{-1}$ in group IV and 600 (260–1160) $\mu\text{g kg}^{-1}$ in group SC) did not differ significantly between the groups. To assess efficacy, we compared the median total pain scores in each group during each 4-h period after operation. There were no significant differences between the groups at any point (fig. 1). Two children in group IV and three children in group SC received one supplementary bolus of diamorphine for inadequate analgesia at the maximum infusion rate.

There were no significant differences between the groups in the incidence of vomiting, excessive sedation or hypoxic episodes. Five patients in group IV and seven patients in group SC vomited.

Excessive sedation was defined as a sedation score of 2 or 3; a score of 2 occurred on two occasions in one patient in group IV and on seven occasions in two patients in group SC. All episodes of excessive sedation occurred during the first postoperative day while the infusion rate was $20 \mu\text{g kg}^{-1} \text{h}^{-1}$. A hypoxic episode was defined as SpO_2 less than 94%; there were 14 episodes in four patients in group IV and 18 episodes in five patients in group SC.

Two cannulae in group IV and no cannulae in group SC needed to be replaced during the diamorphine infusion.

Comment

We have observed that the s.c. route of administration is as effective as the i.v. route for infusion of diamorphine in children after elective surgery. Although s.c. administration has been shown to provide analgesia [3] in children, it has not been shown previously to be as effective as the i.v. route.

The fact that equivalent analgesia can be provided by this route with similar doses of diamorphine and no increase in the incidence of side effects suggests that this technique may be useful in children receiving other opioids by infusion. Use of the s.c. route for opioid infusions is likely to reduce the practical difficulties associated with the provision of this form of analgesia in small children. Intermittent injections of opioid through an indwelling s.c. cannula may be used instead of an infusion but, in common with intermittent i.m. injections, may result in periods of unrelieved pain alternating with episodes of sedation or nausea induced by high plasma concentrations of opioid after bolus dose administration. There was no blinding of observers to the type of infusion used in this study and there is the possibility of bias in the recordings. Furthermore the method of pain assessment used (observer scoring) is not as satisfactory as patient self-report and must be considered to be a relatively insensitive discriminator between analgesic regimens.

It should be noted that the subjects in this study were elective normovolaemic patients. The s.c. route would be contraindicated in patients with or at risk of developing poor peripheral perfusion when there would be a risk of accumulation of opioid at the infusion site resulting in poor analgesia and subsequent absorption of this depot to give the equivalent of a large uncontrolled bolus of opioid.

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Comparison of patient-controlled analgesia in children by i.v. and s.c. routes of administration

E. DOYLE, N. S. MORTON AND L. R. McNICOL

SUMMARY

Sixty children undergoing appendicectomy were allocated randomly to receive one of two PCA regimens with morphine. Group IV received standard i.v. PCA with a bolus dose of morphine $20 \mu\text{g kg}^{-1}$ and a background infusion of $4 \mu\text{g kg}^{-1} \text{h}^{-1}$ while group SC received PCA by the s.c. route with a bolus dose of morphine $20 \mu\text{g kg}^{-1}$ and a background infusion of $5 \mu\text{g kg}^{-1} \text{h}^{-1}$. In both groups there was a lockout interval of 5 min. Group SC self-administered significantly less morphine ($P < 0.05$) and had a significantly ($P < 0.01$) greater percentage of valid demands for analgesia than group IV. There were no differences in pain scores between the groups at rest or during movement. Group IV suffered significantly ($P < 0.01$) more hypoxic episodes than group SC. There were no differences between groups in the incidence of postoperative nausea and vomiting or oversedation. S.c. PCA appears to be as effective and safe as i.v. PCA. By giving patients feedback on the occurrence of valid demands for analgesia, s.c. PCA may produce more appropriate and effective use of PCA. (Br. J. Anaesth. 1994; 72: 533-536)

KEY WORDS

Analgesia: paediatric. Analgesia: patient-controlled.

Patient-controlled analgesia (PCA) is now used commonly for the treatment of acute pain in selected children [1-6]. All reported studies have used the i.v. route of administration. The disadvantages of this route include the need for a dedicated i.v. cannula which may be a particular problem in children or the need for a one-way anti-reflux valve in the i.v. tubing, which is more expensive than a dedicated cannula. In children, the use of an anti-reflux valve makes the junction of the i.v. tubing and the cannula bulky and awkward.

The s.c. route of administration is very satisfactory for opioid infusions in acute [7-9] and chronic [10, 11] pain and also for bolus doses [12]. If the s.c. route of administration could be shown to be suitable for PCA, this would offer potential advantages by avoiding the need for either an anti-reflux valve or a dedicated i.v. cannula. These advantages would be particularly marked in children and in patients where veins are at a premium, such as those with extensive burns and those with chronic or terminal pain.

This study was performed to compare the s.c. and i.v. routes of administration for PCA in children. Both groups received a small background infusion which has been shown to be superior to a PCA regimen with no background infusion [13]. The study included assessment of pain during movement which has been shown to be a more sensitive discriminator between analgesic regimens than assessments carried out at rest [14].

PATIENTS AND METHODS

The study was approved by the hospital Ethics Committee and written informed parental consent was obtained for all patients. We studied 60 children aged 6-14 yr undergoing appendicectomy. On the basis of previous work using these methods [14], it was calculated that the study had a 90% probability of detecting differences in pain scores and side effects which were significant at the 5% level. Patients were visited before operation when the principles of using PCA were explained to the child and parents. Patients were taught to use the trigger of the PCA machine during this visit. Patients were not studied if they had received analgesia before operation.

All patients received a standard general anaesthetic which comprised a rapid sequence induction with thiopentone $5-7 \text{ mg kg}^{-1}$ and suxamethonium 1 mg kg^{-1} . The trachea was intubated and the patients' lungs ventilated with 67% nitrous oxide and 0.5-2.0% isoflurane in oxygen. Neuromuscular block was maintained with vecuronium 0.1 mg kg^{-1} . Morphine 0.1 mg kg^{-1} was given during operation. At the end of surgery, neuromuscular block was antagonized with neostigmine and glycopyrronium in appropriate doses. In the recovery area, patients were titrated to comfort with bolus doses of morphine $50 \mu\text{g kg}^{-1}$, if required.

Before patients left the recovery area, the PCA pump was connected (Graseby, PCAS). Patients were allocated randomly (by means of a computer generated list) to receive one of two different PCA regimens. One group received i.v. PCA (group IV) and the other received PCA by the s.c. route (group

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TABLE I. Patient data and details of morphine consumption (mean (SD or range)). * $P < 0.05$, ** $P < 0.01$

	Group IV	Group SC
Gender (M/F)	17/13	14/16
Age (months)	128.6 (83–168)	131.3 (78–169)
Weight (kg)	39.2 (11.4)	36.6 (8.9)
Duration of PCA use (h)	40.5 (11.9)	40.4 (11.5)
Morphine consumption		
Total (including background infusion)		
$\mu\text{g kg}^{-1}$	1436 (654)	1122 (673)*
$\mu\text{g kg}^{-1} \text{ h}^{-1}$	31.2 (11.1)	27.6 (14.3)*
Self-administered by PCA		
$\mu\text{g kg}^{-1}$	1250 (641)	920 (648)*
$\mu\text{g kg}^{-1} \text{ h}^{-1}$	27.2 (11.1)	22.6 (14.3)*
% Valid demands	71.6 (18.6)	90.5 (8.4)**

SC). In group IV the solution used contained morphine 1 mg kg^{-1} diluted to 50 ml with 0.9% saline to give a concentration of $20 \mu\text{g kg}^{-1} \text{ ml}^{-1}$. The PCA syringe was attached to the side arm of a Cardiff anti-reflux valve incorporated into the i.v. infusion cannula. This group received bolus doses of $20 \mu\text{g kg}^{-1}$ (1 ml) with a lockout interval of 5 min and a background infusion of $4 \mu\text{g kg}^{-1} \text{ h}^{-1}$ (0.2 ml h^{-1}).

In group SC, a 22-gauge catheter was sited s.c. over the deltoid muscle of the same (non-dominant) arm as the i.v. cannula. This cannula was flushed with 1 ml of 0.9% saline and secured with Elastoplast tape. The PCA syringe was attached to this cannula. In group SC the solution used contained morphine 1 mg kg^{-1} diluted in 20 ml of 0.9% saline to give a concentration of $50 \mu\text{g kg}^{-1} \text{ ml}^{-1}$. This group received bolus doses of $20 \mu\text{g kg}^{-1}$ (0.4 ml) with a lockout interval of 5 min and a background infusion of $5 \mu\text{g kg}^{-1} \text{ h}^{-1}$ (0.1 ml h^{-1}). This background infusion differed from that used in group IV because it was not possible to give the same infusion with the dilution of morphine used.

After operation patients breathed air. A monitoring procedure described previously [15] was used. This involved high dependency nursing care with continuous pulse oximetry and hourly recordings of ventilatory frequency and scores for sedation, pain and nausea. The number of demands made, the number of valid demands and the volume of solution infused were also recorded hourly. Patients were reviewed three times a day by one of the authors. Patients were asked to quantify the delay between pressing the trigger of the PCA pump and the onset of analgesia. Patients were also asked about the presence of pain or discomfort at the cannula site and its relation to pressing the PCA trigger. There was always an anaesthetist available to deal with any problems relating to the PCA regimen. PCA was discontinued when there was a consistent decline in use and patients were able to take oral analgesics. At discontinuation of the s.c. PCA, the cannula was removed and the site inspected.

Pain was scored using a four-point, self-reporting score, which has been validated previously [14, 16], as follows: 1 = no pain; 2 = not really sore; 3 = quite sore; 4 = very sore. Assessments were made both at rest and during a specified movement (vital capacity breath followed by a cough). Children were

not wakened from sleep for assessment unless the nurse suspected oversedation and "A" was recorded on the chart at these times. Sedation was scored using a four-point scale as follows: 0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open when shaken; 3 = unrousable. Nausea was scored on a four-point scale: 0 = none; 1 = nausea only; 2 = vomited once in the past 1 h; 3 = vomited more than once in the past 1 h.

If a pain score of > 4 , or a sedation or nausea score of 3 was recorded, an anaesthetist was asked to see the patient.

Results were analysed using the Mann-Whitney U test for pain scores and morphine consumption and chi-square tests for comparison of events between groups.

RESULTS

Patient data are shown in table I. The two groups were similar in age, weight, gender distribution and duration of PCA use. Patients in group IV self-administered significantly more morphine than those in group SC ($P < 0.05$). Group SC had a significantly greater percentage of valid demands than group IV ($P < 0.01$).

Pain scores were compared by calculating the median total pain score during each 4-h period after operation and comparing the groups during each of these periods (at rest and during movement). Figure 1 shows the pain scores in the two groups. There were no significant differences between the groups at rest or during movement at any of these times.

There were significantly more SpO_2 recordings of less than 94% in group IV than in group SC ($P < 0.01$) (table II). SpO_2 readings were regarded as valid and recorded only if they persisted over a period of 5 min, if there was a good pulse signal on the oximeter screen and artefacts caused by poor positioning or venous engorgement had been excluded. The least values recorded were 85% in group IV and 87% in group SC.

There were no significant differences in the incidence of postoperative nausea and vomiting or of oversedation (sedation score of 2 = eyes open to shake or 3 = unrousable) in the two groups (table II). There were no sedation scores of 3 in any patient.

Twenty-eight patients in group SC were aware of bolus infusions shortly after making a demand. Five

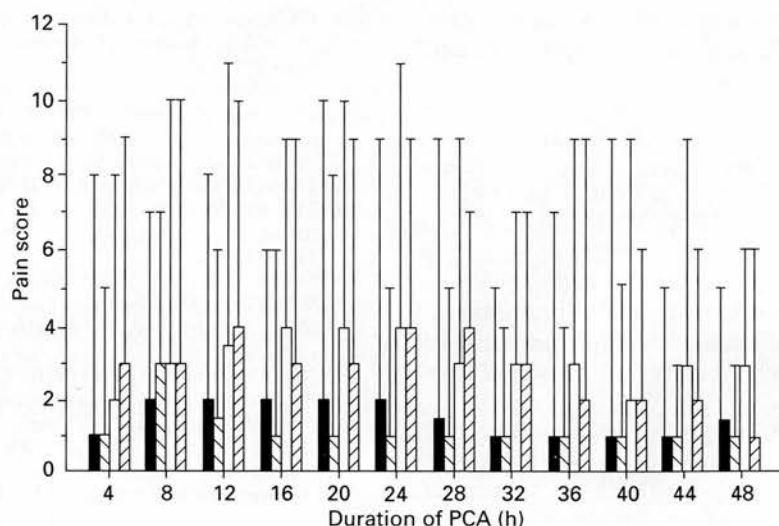


FIG. 1. Median (range) 4-hourly pain scores at rest and during movement for the two groups. ■ = Group IV at rest; □ = group SC at rest; ▨ = group IV during movement; ▩ = group SC during movement.

TABLE II. Incidence of hypoxic episodes (SpO_2 recordings of less than 94%), postoperative nausea and vomiting (PONV) and oversedation in groups IV and SC. ** $P < 0.01$ (chi-square = 8.3)

	Group IV	Group SC
$SpO_2 < 94\%$	193	123**
$SpO_2 \geq 94\%$	1202	1090
PONV present	95	65
PONV absent	1300	1148
Sedation score of 2	10	8
Sedation score of 0 or 1	1385	1205

patients in group SC complained of pain at the cannulation site during bolus infusion. In all of these five patients, bolus doses stopped being painful after several hours of PCA use. Four patients in group IV were able to feel bolus infusions. No patients in this group complained of pain during bolus infusions.

When asked to comment on the interval between making a demand and subsequent analgesia, 25 patients in group SC and 15 patients in group IV described this delay as being less than 5 min.

In group SC, nine patients had a localized erythematous flare at the cannulation site which started soon after commencement of PCA. In all cases this faded after several hours. In group SC, no problems were observed at the s.c. site after removal of the cannula.

DISCUSSION

This study has shown that s.c. PCA appeared to be as effective and safe for acute postoperative pain as i.v. PCA. It also suggested that the s.c. route may have advantages over the i.v. route. There was a lesser consumption of morphine (in patients undergoing the same procedure) associated with a greater proportion of valid demands for analgesia. This was possibly because of the fact that with s.c. PCA, the patient was aware of bolus infusions and the demand for analgesia had been successful. Because of this, patients expected the demand to produce analgesia and tended not to make further invalid demands during the lockout period. The usefulness of a

positive feedback to the patient that a demand has been successful has been noted previously [17, 18] and PCA pumps which produce different sounds after valid and invalid demands for analgesia are being developed. It should be remembered that group SC received a background infusion of $5 \mu\text{g kg}^{-1} \text{h}^{-1}$ (compared with $4 \mu\text{g kg}^{-1} \text{h}^{-1}$ in group IV) and this may have been partly responsible for a reduced requirement for self-administered morphine in group SC. This would not, however, explain the reduction in total morphine consumption in group SC compared with group IV.

The reduction in hypoxic episodes during s.c. PCA compared with i.v. PCA may reflect two possible mechanisms. The reduction in morphine consumption during s.c. PCA may result in less ventilatory depression than would otherwise be the case. Alternatively, differences in the pharmacokinetics of the two routes of administration may result in lesser peak concentrations of morphine if boluses are given s.c. rather than i.v. Limited data [19] concerning the absorption of morphine during i.v. and s.c. infusions in adults suggest that both routes are equally effective but there are no data concerning absorption after intermittent bolus administration. The fact that there was no difference between the groups in the incidence of oversedation suggests that morphine consumption in group IV was not excessive.

In patients breathing air, pulse oximetry is a sensitive monitor of ventilation [20]. Consideration of the ideal alveolar gas equation shows that with an inspired oxygen concentration of 21%, a small increase in alveolar carbon dioxide tension produces a decrease in alveolar oxygen tension and consequent hypoxaemia. An arterial oxygen saturation of 94% corresponds to an arterial oxygen tension of approximately 10 kPa and is associated with mild ventilatory impairment in healthy patients. This is a non-specific monitor of ventilation and discrimination between the possible causes (excess opioid and pain) requires assessment of opioid consumption and the level of sedation. A patient who is hypoxic because of

excess opioid will be sedated while a patient in pain will be alert and unwilling to take a deep breath and cough.

Although the s.c. route of administration is very satisfactory for infusion analgesia in chronic and terminal pain and also acute pain, there is concern that absorption of bolus doses is so slow as to make it unsuitable for use with PCA. This proved not to be the case and in all patients the delay in receiving analgesia after a demand was of the order of a few minutes. We did not attempt to assess this interval accurately because of difficulties for patients in judging time accurately during the postoperative period.

In summary, s.c. PCA appears to be as effective and safe as i.v. PCA and it may offer advantages over the i.v. route by providing feedback on successful demands for analgesia and enhancing appropriate use of the machine.

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Prevention of postoperative nausea and vomiting with transdermal hyoscine in children using patient-controlled analgesia

E. DOYLE, G. BYERS, L. R. McNICOL AND N. S. MORTON

SUMMARY

We have studied 40 children aged 6-14 yr undergoing abdominal surgery under general anaesthesia with extradural block; they were allocated randomly to receive transdermal hyoscine (loading dose 140 µg, followed by 5 µg h⁻¹) or placebo for the duration of postoperative analgesia with PCA morphine. There was a significant ($P < 0.001$) reduction in the incidence of postoperative nausea and vomiting in the treated group compared with the placebo group during the first 48 h after operation. The treated group also had a significantly increased incidence of sedation ($P < 0.02$) and dry mouth ($P < 0.01$). (Br. J. Anaesth. 1994; 72: 72-76)

KEY WORDS

Analgesia: patient-controlled, paediatric, postoperative. Analgesics, opioid: morphine. Vomiting: nausea.

Postoperative nausea and vomiting (PONV) occurs in 40-100 % of patients [1-5]. The causes include the effects of premedicant drugs, anaesthetic agents, postoperative analgesics (especially opioids), the surgery itself and the susceptibility of the patient. PONV appears to be a significant problem in patients who use patient-controlled analgesia (PCA) for postoperative pain relief [6] and, although distressing for a number of children using this form of postoperative analgesia, PONV appears to be less of a problem in children using PCA than it is in adults [7-10].

Several agents with different modes of action are used commonly to treat PONV, including phenothiazines, butyrophenones, antihistamines, dopamine antagonists and anticholinergics. Children are sensitive to the extrapyramidal effects of some of these drugs [11].

The anticholinergic agent, hyoscine, has been shown to have an antiemetic effect when given i.m. [12, 13]. There is also a preparation of hyoscine in the form of a plaster for transdermal application (Scopoderm TTS (Ciba)) which contains hyoscine 1.5 mg. This releases hyoscine 140 µg soon after application, followed by 5 µg h⁻¹ for up to 72 h while the plaster is in place, giving an average absorption rate of hyoscine 500 µg in 72 h. The preparation has

been shown to have a significant antiemetic effect in motion sickness [14-16]. Transdermal application of hyoscine offers potential advantages in the prevention of PONV. It produces steady, small plasma concentrations of hyoscine [17] and avoids the problems of a short half-life, brief duration of action and large peak plasma concentrations which occur after i.m. injection. In paediatric practice the avoidance of i.m. injections is a particular advantage [18].

We have undertaken a prospective, placebo-controlled, double-blind assessment of the efficacy of transdermal hyoscine in preventing PONV in children using PCA morphine after abdominal surgery.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and informed written consent was obtained from the parents of children participating in the study. We studied 40 children aged 6-14 yr undergoing abdominal surgery. Exclusion criteria included inability to operate a PCA machine, unsuitability for extradural anaesthesia and the use of centrally acting or antiemetic drugs within the previous 1 week. Based on previous studies showing the efficacy of this preparation of hyoscine in reducing PONV, we calculated a 90 % probability of finding a difference between the groups which would be significant at the 5 % level. Patients were instructed before operation in the use of a PCA machine for postoperative analgesia.

A standard anaesthetic technique was used for all patients. Premedication comprised diazepam 0.3 mg kg⁻¹ orally, 2-4 h before operation. Anaesthesia was induced with propofol 3 mg kg⁻¹ (plus lignocaine 0.2 mg kg⁻¹) and vecuronium 0.1 mg kg⁻¹. The trachea was intubated and the lungs ventilated with 67 % nitrous oxide in oxygen, with 0.5-2.0 % isoflurane as indicated clinically. The patient was

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then turned to the lateral position and a single extradural injection of 0.25% bupivacaine 2 mg kg⁻¹ (maximum 75 mg) given in the lumbar region. At the end of surgery, residual neuromuscular block was antagonized with neostigmine and glycopyrronium in appropriate doses.

Patients were allocated randomly, by means of computer-generated randomization, to two groups of 20 patients. Group H (hyoscine) received a hyoscine patch and group P (placebo) received an inactive patch. After the induction of anaesthesia and before the start of surgery, patients in group H had a hyoscine patch applied to the skin in the left postauricular area and this was covered with an Elastoplast dressing. Patients in group P had the dressing alone applied to the postauricular skin.

Before the patient left the recovery area, the PCA machine was connected (Graseby PCAS). The solution used consisted of morphine 1 mg kg⁻¹ diluted in 50 ml of normal saline to give a dilution of 20 µg kg⁻¹ ml⁻¹. The PCA machine was attached to the side arm of a Cardiff one-way valve incorporated into the i.v. infusion cannula. The settings used were a bolus dose of 1 ml (20 µg kg⁻¹), with a lockout interval of 5 min. There was no background infusion. If necessary, the patient was given increments of morphine 50 µg kg⁻¹ in the recovery area.

After operation, the patient breathed air. We used a monitoring procedure described previously [19]; this involved a high dependency level of nursing care with hourly recordings of SpO₂, ventilatory frequency, sedation score, pain score and nausea score. The number of demands made and the volume of solution infused by the PCA machine were recorded hourly. PCA was discontinued when the patient was able to take oral analgesics and there was a consistent decline in analgesic use.

Pain was scored using a four-point, self-reporting score which has been validated previously [20]: 0 = no pain; 1 = not really sore; 2 = quite sore; 3 = very sore.

Children were not woken from sleep unless the nurse suspected oversedation; "A" was recorded on the chart at these times. Sedation was scored using a four-point scale: 0 = eyes open spontaneously; 1 = eyes open to speech; 2 = eyes open to shake; 3 = unrousable.

Nausea and vomiting were scored using a four-point scale: 0 = no nausea or vomiting; 1 = nausea only; 2 = vomited once in the past 1 h; 3 = vomited more than once in the past 1 h.

The patient was questioned on each day after operation for the presence of dry mouth and blurred vision. All assessments were made by staff who were unaware if the patient had received hyoscine or placebo.

Prochlorperazine was prescribed for use in both groups if an antiemetic was considered necessary to treat persistent nausea or vomiting. The hyoscine or placebo patches were removed at the time of discontinuation of PCA.

Results were analysed using the unpaired *t* test for patient data, the Mann-Whitney *U* test for pain scores and morphine consumption and chi-square tests for comparisons of events between groups.

RESULTS

Patient data and details of surgery and morphine consumption are shown in table I. Of the laparotomies performed, six in group H and seven in group P involved bowel surgery.

There was a significant reduction in the incidence of PONV in group H compared with group P (*P* < 0.001) during the period of postoperative use of PCA (table II) (for the purposes of analysis, PONV was considered to be present if a nausea score other than 0 was recorded at the hourly recordings). There was a significant antiemetic effect of hyoscine in patients aged less than 10 yr and in those aged 10 yr or more. There was also a significant reduction in the number of patients who complained of PONV at any time during the postoperative period in group H (*P* < 0.05) compared with group P (table II). Six patients in group P and three in group H vomited on one or more occasions.

When the antiemetic effect of hyoscine was analysed for each 24-h period of use there was a significant (*P* < 0.01) antiemetic effect during the first 24 h of use, a significant (*P* < 0.01) antiemetic effect in group H compared with group P during the second 24 h after operation and no significant antiemetic effect in group H compared with group P during the third 24 h after operation (table III).

Two patients in group P received one dose each of prochlorperazine (Stemetil) i.v. during PCA usage.

There were no significant differences between the groups in pain scores at any time during the postoperative period.

TABLE I. Patient data and details of morphine consumption (mean (SD))

	Group H	Group P
Sex (M/F)	6/14	7/13
Age (months)	134 (76-169)	122 (86-171)
Weight (kg)	39.5 (13.4)	36.9 (11.9)
Duration of anaesthesia (min)	101 (41)	108 (44)
Duration of surgery (min)	80 (36.4)	79 (40.4)
Duration of PCA use (h)	50 (9.9)	48 (14.6)
Morphine consumption (µg kg ⁻¹)	1410 (734)	1190 (872)
(µg kg ⁻¹ h ⁻¹)	27.6 (12.5)	22.9 (11.0)
Surgery		
Nephrectomy	6	4
Pyeloplasty	1	1
Mitroffanoff	2	3
Reimplantation of ureters	3	1
Bladder neck repair	2	0
Laparotomy	6	11

TABLE II. PONV in groups H and P: incidence during PCA usage (assessed by hourly nausea scores) and at any time in the postoperative period. †For difference in group H compared with that in group P

	Group H	Group P	χ ² , <i>P</i>
During PCA			
Present	29	69	21.3, < 0.001†
Absent	646	554	
Any time after op.			
Present	6	14	4.9, < 0.05†
Absent	14	6	

TABLE III. Incidence of PONV in groups H and P during the first, second and third 24-h periods after operation. †For reduction in group H compared with that in group P

	Group H	Group P	χ^2 , P
First 24 h			
Present	20	45	8.9, < 0.01†
Absent	268	264	
Second 24 h			
Present	8	17	6.9, < 0.01†
Absent	317	225	
Third 24 h			
Present	1	5	2.7, > 0.05†
Absent	65	63	

TABLE IV. Side effects in groups H and P: incidence of oversedation, Sp_{O_2} readings less than 94%, dry mouth during the second and third days after operation and blurred vision after operation. *Between groups

	Group H	Group P	χ^2 , P
Sedation score 2	32	15	5.8, < 0.02*
Sedation score 0 or 1	963	952	
Sp_{O_2} < 94%	136	117	2.1, > 0.10*
Sp_{O_2} \geq 94%	810	850	
Dry mouth	19	9	9.6, < 0.01*
No dry mouth	1	11	
Blurred vision	1	0	0.0, > 0.05*
No blurred vision	19	20	

The number of occasions on which patients were considered to be excessively sedated (sedation scores of 2 = eyes open to shake; 3 = unrousable) was significantly ($P < 0.02$) greater for score 2 in group H (table IV). There were no scores of 3 in either group.

There was no significant difference between the groups in the number of occasions on which Sp_{O_2} less than 94% was recorded (table IV). One patient in group H was excluded from this analysis because he was receiving supplementary oxygen as a result of a pneumothorax produced during a nephrectomy.

There was no significant difference in the incidence of dry mouth during the first day after operation, but during the second and third days there was a significantly greater incidence of this symptom in group H ($P < 0.01$) (table IV).

There was no significant difference in the incidence of blurred vision between groups during the postoperative period (table IV).

One child in group H suffered hallucinations when the hyoscine patch had been in place for 36 h. This responded quickly to removal of the patch and cleaning of the application site. There were no local reactions at the site of patch application in any patient.

DISCUSSION

In this study we have found a significant antiemetic effect of transdermal hyoscine. Children generally suffer less from PONV than adults when PCA is used: the incidence varies from 4% to 34% [7–10] compared with 38–82% in adults [6, 21, 22]. Although the majority of nausea scores in our

placebo group were 0, this reflects the frequency of observation. More than 67% of patients in group P suffered from PONV, which is a distressing symptom in many patients.

The use of propofol as an induction agent, followed by inhalation agents, causes less PONV than thiopentone [23–25] and it has been suggested that propofol has antiemetic effects [26]. Avoidance of preoperative opioid premedication and intraoperative opioids is likely to reduce total opioid consumption. An extradural block provides analgesia into the postoperative period and reduces the requirements for PCA morphine in the early postoperative period.

It has been suggested that transdermal hyoscine should be applied several hours before surgery [27], so that therapeutic plasma concentrations are attained perioperatively. It is possible that a more marked antiemetic effect would have been found if we had done this rather than apply the patches at induction of anaesthesia. The time to first tolerating oral fluids is often regarded as a useful indicator of the duration and impact of PONV, but it is not a precise indicator, as it is influenced by individual ward routines, and for this reason was not adopted in our study.

Other studies of the efficacy of transdermal hyoscine in the prevention of PONV are contradictory. Two studies [21, 22] used transdermal hyoscine in combination with PCA after intra-abdominal gynaecological surgery without regional block. The first [21] found a reduction in PONV immediately after operation and on the third day after operation. The treated group required 50% of the number of supplementary doses of antiemetic as those in the placebo group. Preoperative opioids were omitted and fentanyl was given during operation. The other study [22] found a significant antiemetic effect of transdermal hyoscine compared with placebo and a reduced need for supplementary droperidol in the treated group. There was no opioid premedication and fentanyl was given during operation.

Two studies [28, 29] in patients receiving extradural morphine for postoperative analgesia showed that transdermal hyoscine had a significantly greater antiemetic effect than placebo, with a reduced requirement for supplementary antiemetics. One of these [28] examined patients undergoing intra-abdominal gynaecological surgery with general anaesthesia and intraoperative extradural block and the other [29] was in women undergoing Caesarean section with extradural block.

Transdermal hyoscine has also been found to be effective after orthopaedic and plastic surgery [30]. In contrast, Koski and colleagues [31] found no effect of transdermal hyoscine on the incidence of PONV in female patients. However, this study was not well controlled. Tigerstedt, Salmela and Aromaa [32] also found transdermal hyoscine was no more effective than placebo or intraoperative droperidol in preventing PONV. In this study, a range of surgical procedures was involved, the hyoscine patch was applied only 50 min before surgery, an opioid premedication was given in addition to intra-

operative fentanyl, and postoperative analgesia was with i.m. opioids.

The finding of an increased incidence of dry mouth in our patients in group H is in keeping with the results of several previous studies [22, 29–31, 33]. We found no difference between groups H and P in the incidence of dry mouth on the first day, probably because of the high incidence of this symptom in all patients soon after abdominal surgery, as a result of preoperative fasting and tracheal intubation.

Other studies have reported visual disturbances induced by hyoscine used for both travel sickness [14] and after operation [5, 21, 31–33]. We found no difference in the incidence of this symptom between groups H and P. This may be because children are less affected, or because this symptom is less troublesome to children.

Psychosis has been reported after transdermal hyoscine [34, 35] in adults and children. It is unusual, and treated easily by removal of the patch and cleaning of the skin.

In summary, we have found a useful antiemetic effect of transdermal hyoscine during the first 48 h after operation in children undergoing abdominal surgery with balanced anaesthesia when postoperative analgesia was provided by PCA morphine. Use of the hyoscine patch was associated with an increase in the incidence of sedation and dry mouth.

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